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Certolizumab pegol (CDP870) for rheumatoid arthritis in adults (Review)

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[Intervention Review]

Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

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ABSTRACT

Background

Tumour necrosis factor (TNF)-alpha inhibitors are beneficial for the treatment of rheumatoid arthritis (RA) in terms of reducing the risk of joint damage, improving physical function and improving quality of life. This Cochrane review is an update of a review of the treatment of RA with certolizumab pegol that was first published in 2011.

Objectives

To assess the clinical benefits and harms of certolizumab pegol (CDP870) in patients with RA who have not responded well to conventional disease-modifying anti-rheumatic drugs (DMARDs).

Search methods

We searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2014, Issue 5), MEDLINE, EMBASE, Scopus, TOXLINE, Web of Knowledge; websites of the US Food and Drug Administration (FDA) and European Medicines Evaluation Agency (EMEA); reference lists of articles; and searched http/clinicaltrials.gov. The searches were updated from 2009 (date of last search for the original review) to 5 June 2014.

Selection criteria

Randomised controlled trials that compared certolizumab pegol with any other agent including placebo or methotrexate (MTX) in adult patients with active RA despite current or prior treatment with conventional disease-modifying anti-rheumatic drugs (DMARDs), such as MTX.

Data collection and analysis

Two authors independently assessed search results, trial quality and extracted data. Disagreements were resolved by discussion or referral to a third author.

Main results

Eleven trials were included in this update. Ten (4324 patients) were included in the pooled analysis for benefits, five more than previously, and 10 (3711 patients) in the pooled analysis for harms, four more trials (1930 patients) than previously. The duration of follow-up varied from 12 to 52 weeks and the range of doses of certolizumab pegol varied from 50 to 400 mg given subcutaneously (sc). In phase III trials, the control was placebo plus MTX in five trials and placebo in four trials. The risk of bias of the included studies was assessed as low but there may have been a risk of attrition bias.

Statistically significant improvements were observed at 24 weeks with the approved dose of 200 mg certolizumab pegol every other week, in 1) American College of Rheumatology (ACR) 50% improvement: 27% absolute improvement (95% CI 20% to 33%), NNT of 4 (95% CI 3 to 8), risk ratio (RR) 3.80 (95% CI 2.42 to 5.95); 2) the Health Assessment Questionnaire (HAQ): -12% absolute improvement (95% CI -9% to -14%), NNT of 6 (95% CI 5 to 8), mean difference (MD) - 0.35 (95% CI -0.43 to -0.26) (scale 0 to 3); 3) Disease Activity Score (DAS) remission improvement: absolute improvement 11% (95% CI 8% to 15%), NNT of 9 (95% CI 4 to 20), RR 8.47 (95% CI 4.15-17.28); and 4) radiological changes: erosion score (ES) absolute improvement -0.29% (95% CI -0.42% to -0.17%), NNT of 6 (95% CI 4 to 10), MD -0.67 (95% CI -0.96 to -0.38) (scale 0 to 230). Serious adverse events were statistically significantly more frequent for certolizumab pegol (200 mg every other week) with an absolute rate difference of 4% (95% CI 2% to 6%), NNTH of 32 (95% CI 17 to 88), Peto odds ratio (OR) 1.77 (95% CI 1.27 to 2.46). There was a statistically significant increase in all withdrawals in the placebo groups (for all doses and all follow-ups) with an absolute rate difference of -34% (95% CI -18% to -50%), NNTH of 4 (95% CI 3 to 5), NNTH of 4 (95% CI 3 to 5), RR 0.42 (95% CI 0.36 to 0.50); and there was a statistically significant increase in all withdrawals due to adverse events in the certolizumab groups (for all doses and all follow-up) with an absolute rate difference of 2% (95% CI 1% to 3%), NNTH of 55 (95% CI 27 to 238), Peto OR 1.66 (95% CI 1.15 to 2.37).

The risk of bias was low and the quality of evidence was downgraded to moderate because of high rates of dropouts (> 20%) in most of the trials. We did not find any problems with inconsistency, indirectness, imprecision or publication bias.

Authors' conclusions

The results and conclusions did not change from the previous review. There is moderate-level evidence from randomised controlled trials that certolizumab pegol alone or combined with methotrexate is beneficial in the treatment of RA. Adverse events were more frequent with active treatment. We found a potential risk of serious adverse events.

PLAIN LANGUAGE SUMMARY

Certolizumab pegol for treating adults with rheumatoid arthritis

We conducted an updated review of the effect of certolizumab pegol for adults with RA. We searched all relevant studies until June 2014 and found 11 studies with 4324 people.

In people with rheumatoid arthritis:

- certolizumab pegol probably improved the American College of Rheumatology ACR50 (pain, function and other symptoms of RA), health-related quality of life, and the chance of remission of RA,

- certolizumab pegol probably reduced joint damage as seen on the x-ray,

- certolizumab pegol probably increased serious adverse events,

- with certolizumab pegol fewer people stopped taking their treatment, but most of these people stopped due to serious adverse events.

What is rheumatoid arthritis and what is certolizumab pegol?

When you have RA your immune system becomes overactive and attacks the lining of your joints. This makes your joints swollen, stiff and painful. There is no cure for RA at present, so the treatments aim is to relieve pain and stiffness and improve your ability to move.

Certolizumab pegol works by blocking a substance produced by the body known as tumour necrosis factor alpha (TNF). Certolizumab pegol is given by injections under the skin, either by patients themselves or someone else.

What happens to people with rheumatoid arthritis who take certolizumab pegol 200 mg every other week after six months?

ACR50 (a 50% improvement in the number of tender or swollen joints and other outcomes such as pain and disability):

- 27 more people out of 100 experienced improvement in the symptoms of their rheumatoid arthritis after six months with certolizumab pegol (absolute improvement 27%),

- 36 people out of 100 who took certolizumab pegol experienced improvement compared to 9 people out of 100 who took a placebo (a fake injection).

Health-related quality of life (Health Assessment Questionnaire):

- the additional benefit on this questionnaire for people who took certolizumab pegol was a change of -0.35 units on a scale 0 to 3 units (with 3 indicating a worse health state, therefore a negative change indicates improvement) (absolute improvement 12%),

- people on certolizumab pegol who completed the Health Assessment Questionnaire (HAQ) had a change of -0.48 points on a scale of 0 to 3 compared to a change of -0.13 points on a scale of 0 to 3 for people who took a placebo.

Remission (absence of clinical signs of inflammation):

- 11 more people out of 100 experienced remission with certolizumab pegol (absolute improvement 11%),

- 13 people out of 100 who took certolizumab pegol experienced remission compared to 2 people out of 100 who took a placebo.

Radiological changes (x-rays of the joints):

- the joint damage in people who took certolizumab pegol was 0.07 units less on a scale of 0 to 230 units (absolute improvement -0.29%),

- the damage to joints in people who took certolizumab pegol was 0.04 units less on a scale of 0 to 230 units compared to people who took a placebo whose joint damage was 0.7 units more on a scale of 0 to 230 units.

Serious adverse events:

- 4 more people out of 100 experienced serious adverse events with certolizumab pegol (4% absolute harm),

- 8 people out of 100 who took certolizumab pegol experienced serious adverse events compared to 4 people out of 100 who took a placebo.

What happens after 52 weeks to people with rheumatoid arthritis who take certolizumab pegol 200 mg and certolizumab 400 mg?

All withdrawals:

- 33 less people out of 100 stopped taking their treatment after 52 weeks with certolizumab pegol compared with placebo (absolute improvement 34%),

- 23 people out of 100 who took certolizumab pegol stopped taking their treatment compared to 56 people out of 100 who took placebo.

Withdrawals due to adverse events:

- 2 more people out of 100 stopped taking their treatment due to adverse events after 52 weeks with certolizumab pegol compared with placebo (absolute improvement 2%),

- 5 people out of 100 who took certolizumab pegol stopped taking their treatment due to adverse events compared to 3 people out of 100 who took placebo.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Certolizumab pegol 200 mg sc (with or without MTX) versus placebo (with or without MTX) for rheumatoid arthritis in adults

Patient or population: patients with rheumatoid arthritis in adults
Settings: adults (18 years old or more) who have persistent disease activity despite current or previous use of conventional disease modifying anti-rheumatic drugs (DMARDs)
Intervention: certolizumab pegol 200 mg sc (with or without MTX) versus placebo (with or without MTX)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Summary of findings certolizumab pegol 200 mg sc (with or without MTX) versus placebo (with or without MTX)				
ACR 50% improvement Follow-up: mean 24 weeks	**87 per 1000**	**359 per 1000** (328 to 391)	**RR 3.80** (2.42 to 5.95)	1445 (5 studies)	⊕⊕⊕◯ **moderate**[1,]	Absolute risk difference = 27% (95% CI 20% to 33%). Relative per cent change = 280% (142% to 495%). NNT = 4 (3 to 8)
HAQ change from baseline Scale from: 0 to 3. Follow-up: mean 24 weeks	The mean HAQ change from baseline in the control groups was **0.04**	The mean HAQ change from baseline in the intervention groups was **0.35 lower** (0.43 to 0.26 lower)	**MD -0.35** (-0.43 to -0.26)	1268 (4 studies)	⊕⊕⊕◯ **moderate**[2]	Absolute risk difference = -12% (95% CI -9% to -14%). Relative per cent change = -21% (-15% to -25%). NNT = 6 (5 to 8)

Proportion of patients achieving DAS <2.6 (remission) Follow-up: mean 24 weeks	**16 per 1000**	**126 per 1000** (104 to 149)	**RR 8.47** (4.15 to 17.28)	1381 (4 studies)	⊕⊕⊕○ **moderate**[3]	Absolute risk difference = 11% (95% CI 8% to 15%). Relative per cent change = 747% (315% to 1628%) NNT = 9 (4 to 20)
Radiological changes: Erosion Scores (ES) Scale from: 0 to 230. Follow-up: 24 weeks	The mean radiological changes: Erosion Scores (ES) in the control groups was **23.1**	The mean Radiological changes: Erosion Scores (ES) in the intervention groups was **0.67 lower** (0.96 to 0.38 lower)	**MD -0.67** (-0.96 to -0.38)	859 (2 studies)	⊕⊕⊕○ **moderate**[4]	Absolute risk difference = -0.29% (95% CI -0.42% to -0.17%). Relative per cent change = -2.90% (-4.16% to -1.65%) NNT = 6 (4 to 10)
Serious adverse events Follow-up: 12 to 24 weeks	**45 per 1000**	**78 per 1000** (66 to 90)	**Peto OR 1.77** (1.27 to 2.46)	2729 (7 studies)	⊕⊕⊕○ **moderate**[5]	Absolute risk difference = 4% (95% CI 2% to 6%). Relative per cent change = 77% (27% to 146%). NNTH = 32 (17 to 88)
All Withdrawals: All doses of certolizumab pegol vs placebo Follow-up: 0 to 52 weeks	**561 per 1000**	**226 per 1000** (211 to 241)	**RR 0.42** (0.36 to 0.50)	3962 (10 studies)	⊕⊕⊕○ **moderate**[6]	Absolute risk difference = -34% (95% CI -18% to -50%). Relative per cent change= -58% (-50% to -64%). NNTH = 4 (3 to 5)
Withdrawals due to adverse events All doses of certolizumab pegol versus placebo	**29 per 1000**	**46 per 1000** (39 to 54)	**Peto OR 1.66** (1.15 to 2.37)	3998 (9 studies)	⊕⊕⊕○ **moderate**[7]	Absolute risk difference = 2% (95% CI 1% to 3%). Relative

Follow-up: 0 to 52 weeks			per cent change = 66% (15% to 137%). NNTH = 55 (27 to 238)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] High risk of bias due to > 20% dropout rate in 4 out 5 trials. [2] High risk of bias due to > 20% dropout rate in 3 out 4 trials. [3] High risk of bias due to > 20% dropout rate in 3 out 4 trials. [4] High risk of bias due to > 20% dropout rate in 2 out 2 trials. [5] High risk of bias due to > 20 % dropout rate in 6 out 7 trials. [6] High risk of bias due to > 20% dropout rate in 7 out 10 trials. [7] High risk of bias due to > 20% dropout rate in 8 out 9 trials.

BACKGROUND

Description of the condition

Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting the synovium of joints and other structures like tendon sheaths and bursas. RA typically causes a symmetrical polyarticular arthritis with pain, swelling and stiffness of the affected joints. If disease is not controlled early, damage may become permanent leading to significant disability. Patients commonly experience fatigue and show changes in the blood, such as anaemia due to chronic inflammation, and an acute phase reaction. In some patients organs such as the skin (as rheumatoid nodules), lungs (pleural inflammation and alveolitis), heart (pericarditis), blood vessels (vasculitis) and the eyes (dry eyes or inflammation) may be affected (Tureson 2013). RA is also associated with reduced life expectancy, which is particularly due to cardiovascular disease (Meune 2009) but in the early years also due to pulmonary disease and lymphoma (Young 2007).

Important genetic influences are recognised, in particular genes linked to activation of the immune system (Barton 2009), however environmental factors such as an urban versus a rural environment and smoking are also associated with an increased risk of RA (Edwards 2005). People of all ages are affected but the disease begins most commonly between the ages of 40 and 70 years and the incidence rises with increasing age (Doran 2002). Three times as many women as men are affected and the population prevalence in Western countries is between 0.5% and 1%. Significant functional limitations occur in 15% of patients five years after disease onset and around a third of those in paid work experience work disability (Young 2000). In Spain, RA causes around 10% of total disability and 5% of transitory disability (Carmona 2002) including occupational disability (Doeglas 1995). Moreover, rapid induction of remission translates into maintenance of work capacity (Puolakka 2005).

Description of the intervention

The management of RA has undergone dramatic changes during the last decade. The European League Against Rheumatism has recently released updated recommendations for the management of RA (Smolen 2014). The goal of treatment is to induce remission, defined as the absence of signs and symptoms of significant inflammatory disease activity (Felson 2011). This applies particularly to patients with newer onset RA, whereas in long-standing and refractory disease low disease activity may be acceptable. To meet these objectives, and according to the latest guidance, treatment with disease-modifying anti-rheumatic drugs (DMARDs) should be initiated as soon as a diagnosis of RA is made, and methotrexate (MTX) has been considered (Lopez Olivo 2014) the mainstay of treatment of RA (Singh 2012). The application of new treatment strategies, such as tight control using composite measures of disease activity and appropriate switching of drug treatment when the objectives are not reached, are also highly beneficial approaches (Smolen 2010).

Not infrequently people do not respond to or are unable to tolerate DMARDs (Yee 2003). The newer biological drugs that have been introduced and approved for the treatment of RA in recent decades have been associated with clinical outcome improvement (Singh 2009) but also with higher rates of adverse events (Singh 2011).

How the intervention might work

RA is characterised by immunological activation of many cell types and a network of cytokines, particularly tumour necrosis factor alpha (TNF-alpha) (Brennan 2008). Inhibitors of TNF-alpha have been a major development in the treatment of RA. Randomised trials have shown that these drugs are highly beneficial in patients with RA who have not responded well to conventional DMARDs. TNF-alpha inhibitors have been shown to reduce the risk of joint damage, improve physical function and quality of life (Chen 2006). Five TNF-alpha inhibitors are currently licensed for use in RA in Europe and the US. These are adalimumab (Navarro Sarabia 2005), etanercept (Lethaby 2013), golimumab (Singh 2010), infliximab (Lethaby 2013) and certolizumab pegol (Ruiz Garcia 2011). Comparative efficacy studies to evaluate the potential differences between anti-TNF and non-antiTNF biologics have shown little difference between them (Navarro Millan 2013). One pragmatic, open-label, controlled trial has directly compared etanercept and adalimumab and reported similar persistence rates and efficacy and safety over two years of treatment (Jobanputra 2012). Similar results have been obtained with certolizumab pegol in extension studies, the American College of Rheumatology ACR20 57% and ACR50 27% at 8 years (NCT00160693) and ACR20 81% and ACR50 58% at 7 years (NCT00175877). An important limitation of the wider use of TNF inhibitors is the high cost, between USD 10,000 and USD 25,000 per patient a year.

A systematic review of infliximab and adalimumab showed that the risks of malignancy and serious infection were increased, with odds ratios of 3.3 (95% confidence interval (CI) 1.2 to 9.1) and 2.0 (95% CI 1.3 to 3.1) respectively (Bongartz 2006). However, more recent data showed that therapy with anti-TNF is not related to an increased risk of malignancies (skin cancer, melanoma, lymphoma or solid tumours) (Lopez Olivo 2012). A second review of nine biologic drugs (the five TNF inhibitors etanercept, adalimumab, infliximab, golimumab and certolizumab pegol; the interleukin (IL)-1 antagonist anakinra; the IL-6 antagonist tocilizumab; the anti-CD28 abatacept; and anti-B cell rituximab) showed that biologics as a group were associated with a statistically significant higher rate of total adverse events (odds ratio (OR) 1.28, 95% credible index (CrI) 1.09 to 1.50) and withdrawals due to adverse events (OR 1.47, 95% CrI 1.20 to 1.86), and an increased risk of

tuberculosis (TB) reactivation (OR 4.68, 95% CrI 1.18 to 18.60) compared to control (Singh 2011).

Certolizumab pegol is an anti-TNF consisting of a humanised immunoglobulin fragment (Fab) conjugated to polyethylene glycol (PEG), also termed pegylation. This unique molecular structure yields a longer half-life and reduces the need for frequent dosing (Choy 2002). Certolizumab pegol in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active RA in adult patients when the response to DMARDs including MTX has been inadequate. It also can be given as monotherapy in the case of intolerance, side effects or contraindications to MTX. The drug has been shown to reduce the rate of progression of joint damage as measured by x-ray and to improve physical function. Long-term studies also show persistence rates of 88.9% at two years with 46.7% of patients in low disease activity (Keystone 2012).

Why it is important to do this review

Biological treatment has led to a radical change in the prognosis and quality of life of patients with RA, however clinicians need to take into account the potential risks associated with their use. This review summarises the current data available on the benefits and harms of certolizumab pegol, on its own and in combination with MTX, for the treatment of RA. New evidences concerning efficacy, safety and long-term persistence have become available since the previous review update. It is important to be sure that clinicians choose the treatment for people with RA appropriately using the best medical evidence available.

OBJECTIVES

To assess the clinical benefits and harms of certolizumab pegol (CDP870) in patients with RA who have not responded well to conventional disease-modifying anti-rheumatic drugs (DMARDs).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Adults (18 years of age and older) with RA who have persistent disease activity despite current or previous use of conventional DMARDs.

Patients with RA were defined as those meeting the American College of Rheumatology (ACR) 1987 revised criteria (Arnett 1988) for RA. That is to say, they had to have an active form of the disease as demonstrated by at least two of the following symptoms:

1. three or more tender joint areas as observed by a physician;
2. three or more swollen joint areas as observed by a physician;
3. early morning stiffness with a duration > 30 minutes;
4. acute phase reactants such as a Westergren erythrocyte sedimentation rate (ESR) more than 30 mm/hour or C-reactive protein (CRP) more than 10 mg/mL.

Types of interventions

The intervention was certolizumab pegol (CDP870) at any dose. The comparators were placebo or any DMARD including other biologic agents used to treat RA.

Types of outcome measures

Major outcomes

- The proportion of patients achieving an ACR50
- Health-related quality of life, such as the Health Assessment Questionnaire (HAQ) or Short Form Health Survey (SF-36)
- Disease Activity Score (DAS28 or other versions of DAS)
- Radiological changes (erosion score (ES), modified total Sharp score, joint space narrowing)
- Serious adverse events
- All withdrawals
- Withdrawals due to adverse events

The ACR50 is defined as a 50% improvement in the number of tender and swollen joints and a 50% improvement in at least three of the following items: observer evaluation of overall disease activity, patient evaluation of overall disease activity, patient evaluation of pain, a score of physical disability, or improvements in blood acute-phase responses.

Scores in the HAQ range from 0 to 3, with 3 indicating a worse health state, therefore a negative change indicates improvement. The SF-36 is a scale from 0 to 100 where 0 is the worst and 100 the best health state.

Serious adverse effects were defined as malignancies and all infections, especially tuberculosis and death.

All causes of withdrawals from the medication were sought.

Minor outcomes

- ACR20 and ACR70 (a 20% or 70% improvement respectively in the parameters described above)
- Frequency of adverse events

The following adverse events were sought: headache, fever, blood disorders, laboratory disorders, abdominal pain, nasopharyngitis, nausea, respiratory tract infections, urinary tract infections, neck pain, congestive heart failure, pruritus and anaphylaxis.

Search methods for identification of studies

Electronic searches

The search strategy used the revision of the Cochrane highly sensitive search strategy (HSSS) for PubMed (Glanville 2006), the best sensitivity filter developed by the Hedges Team (Wong 2006a; Wong 2006b) and followed the Cochrane Musculoskeletal Review Group (CMSG) recommendations. Searches included both MeSH headings and text terms for CDP870 and rheumatoid arthritis. The searches were done by Ms Tamara Rader, Trial Search Co-ordinator of the CMSG. These searches included: Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL), HTA, DARE, NHS EED (*The Cochrane Library)* (Appendix 4); MEDLINE (Appendix 1); EMBASE (Appendix 2); CINAHL (Appendix 3); SCOPUS (Appendix 5); TOXLINE (TOXNET) (Appendix 6).
Safety data were obtained from clinical trials.
We updated the searches in CENTRAL (*The Cochrane Library* 2014, Issue 5), MEDLINE (2009 to 5 June 2014), EMBASE (2009 to 5 June 2014), SCOPUS (2009 to 5 June 2014), TOXLINE (2009 to 5 June 2014), Web of Knowledge (2009 to 5 June 2014) and the websites of the US Food and Drug Administration (FDA) and European Medicines Evaluation Agency (EMEA) (2009 to 5 June 2014).

Searching other resources

1. We examined the information made available by the main researchers and sponsors in www.clinicaltrials.org
2. We reviewed information on the clinical trial meta-register database (www.controlled-trials.com/mrct/)
3. We looked for health technology assessment reports from the European, Canadian, North American and Australian national agencies to identify further trials
4. The reference lists of all identified studies were inspected for more trials
5. When published data were missing, incomplete, or inconsistent with the trial protocols, further information was sought from the authors and manufacturers (UCB)

Data collection and analysis

Selection of studies

Two authors independently assessed search results for potential studies that met the inclusion criteria and disagreements were resolved by discussion or referral to a third author.

Inclusion criteria

1. RCTs that compared certolizumab pegol with any other agent including placebo in adult RA patients with active RA despite current or prior treatment with DMARDs
2. Trials that were fully published as a paper or available as a complete trial report. Where published only as abstracts the trial reports were requested from the manufacturers
3. Studies having at least three months of follow-up to assess benefits

To assess harms we also sought studies having a suboptimal length of follow-up, from eight weeks.

Exclusion criteria

1. Trials of certolizumab pegol in juvenile arthritis, Crohn's disease, psoriatic arthritis and other forms of spondyloarthritis
2. Trials of certolizumab pegol comparing different doses or routes of administration without another active or placebo control group (except for assessing harm outcomes)
3. Studies reporting solely on laboratory measures aimed at investigating disease or treatment mechanisms and which did not report relevant clinical outcomes
4. Observational studies of certolizumab pegol
5. Interim results of trials

Data extraction and management

Two review authors independently reviewed titles and abstracts of studies identified in the search to assess which studies might potentially meet the inclusion criteria; where there was doubt, the full article was acquired for further inspection. Potential studies identified by this process were then obtained and two authors independently screened them to see if they met the review criteria using a Web interface. A final table was produced in Excel. We did not need to resolve any disagreements through discussion.
Data were extracted, when possible for intention-to-treat populations, as raw numbers plus any summary measures with the standard deviations, confidence intervals and P values of the outcomes reported. These were compiled in an Excel spreadsheet. Differences of opinion and data discrepancies were to be resolved by reference to a third review author (Sylvia Bort) but that did not happen.

Assessment of risk of bias in included studies

According to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), the risk of bias was assessed by creating a 'risk of bias' table for each study. A summary is presented below as a risk of bias graph.
The main criteria used to assess the risk of bias included: blinding of participants, allocation concealment, random sequence generation, incomplete outcome data, selective reporting of outcomes, and other biases (such as fraud or imbalance in the groups, or the sponsor either owns the data or needed to approve the manuscript). The risk of bias in each study was explicitly judged on the basis of each criterion using the following: low risk of bias, high risk of bias, unclear risk of bias (either lack of information or uncertainty over the potential bias). These criteria were included in the tables. Disagreements were resolved by discussion between the two review authors. If needed a third review author was available for discussion, but there were no disagreements.

Measures of treatment effect

The risk difference was used to quantify the number needed to treat (NNT) (Laupacis 1988). We calculated the NNT from the risk ratio according to the formula NNT = 1/ACR*(1 - RR), where ACR = assumed control risk and RR = risk ratio. When events were very rare (< 10%) we used the Peto odds ratio (Peto OR). For continuous data we used mean differences (MDs) when the results were measured in the same way in the different studies. We used standardised mean differences (SMDs) when the results obtained were conceptually the same but used different measurement scales. The central estimate (mean) and standard deviation were recorded. Where these were not directly stated they were calculated from the standard error or the different means and their respective confidence intervals (CIs) or P values. When medians and interquartile ranges were the only data provided, the median was used as a proxy measure of the mean and the difference between the first and third interquartile was considered equivalent to 1.35 of the SD.

Unit of analysis issues

Most of the clinical trials had a simple parallel group design with participants individually randomised to one of two intervention groups. The unit of analysis was not an issue in this review.

Dealing with missing data

We carried out an intention-to-treat analysis. Every individual allocated to the intervention was counted whether they completed the follow-up or not. We have assumed that those who dropped out had no change in their outcome. This rule is conservative for the response to treatment because it assumes that those discontinuing the studies would not have responded. It is not conservative for adverse effects. However, assuming that all those leaving early had developed side effects could overestimate risk.
When published data were missing, incomplete or inconsistent with the RCT protocols or meeting abstracts, we asked for further information from the authors and manufacturers. We only excluded abstracts of studies that were interim reports of studies that had not yet finished recruiting.

Assessment of heterogeneity

We have explored heterogeneity between the trials using the Chi ^{2} test for heterogeneity, with a 10% level of significance, and the I^2 statistic. We interpreted the ranges of I^2 according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions*: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% considerable heterogeneity (Higgins 2011).

Assessment of reporting biases

We planned to explore reporting bias using funnel plots when doing a meta-analysis for 10 or more studies.

Data synthesis

The need to pool the results according to a fixed-effect or random-effects model analysis was explored (Laird 1990). We planned to use the fixed-effect model to pool the data because statistical heterogeneity in our preview review was not high. However, finally we decided to perform a random-effects model despite the I^2 values being low. Although it was the same drug, there was a clear clinical heterogeneity (different doses, allowing MTX or not, different follow-up, different duration of RA, etc.).
The number needed to treat to benefit (NNTB) and the number needed treat to harm (NNTH) were calculated. The mean difference was used to calculate the benefit (absolute change expressed as both a percentage and in its original units) for continuous outcomes such as HAQ, SF-36 and radiological changes.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were planned for the duration of the illness (approximately three years evolution), patients' sex, drug dose and administration, and methodological quality. If heterogeneity had been detected then a subgroup analysis (Yusuf 1991), or a meta-regression (Thompson 1999), would have been carried out to see if it could be explained.

Sensitivity analysis

We a priori planned the following sensitivity analyses in order to explore effect size differences and the robustness of conclusions.

1. Effect of study quality, dened as blinding of participants, allocation concealment, random sequence generation, incomplete outcome data, selective outcome reporting and other sources of bias.
2. Effect of imputation, size of trials, use of concomitant methotrexate, and doses of certolizumab pegol.

Summary of findings table

We used the 'Grades of Recommendation, Assessment, Development and Evaluation' developed by the GRADE working group to provide an overall grading of the quality of the evidence by outcome. The GRADE approach specifies four levels of quality. The highest quality rating is for RCT. Review authors can, however, downgrade randomised trial evidence from 'high' to 'moderate', 'low' or even 'very low' quality evidence depending on the presence of specific factors: design or implementation, imprecision, inconsistency, indirectness, or reporting bias (see *Cochrane Handbook for Systematic Reviews of Interventions* Chapter XII (section 12.2) (Higgins 2011)).

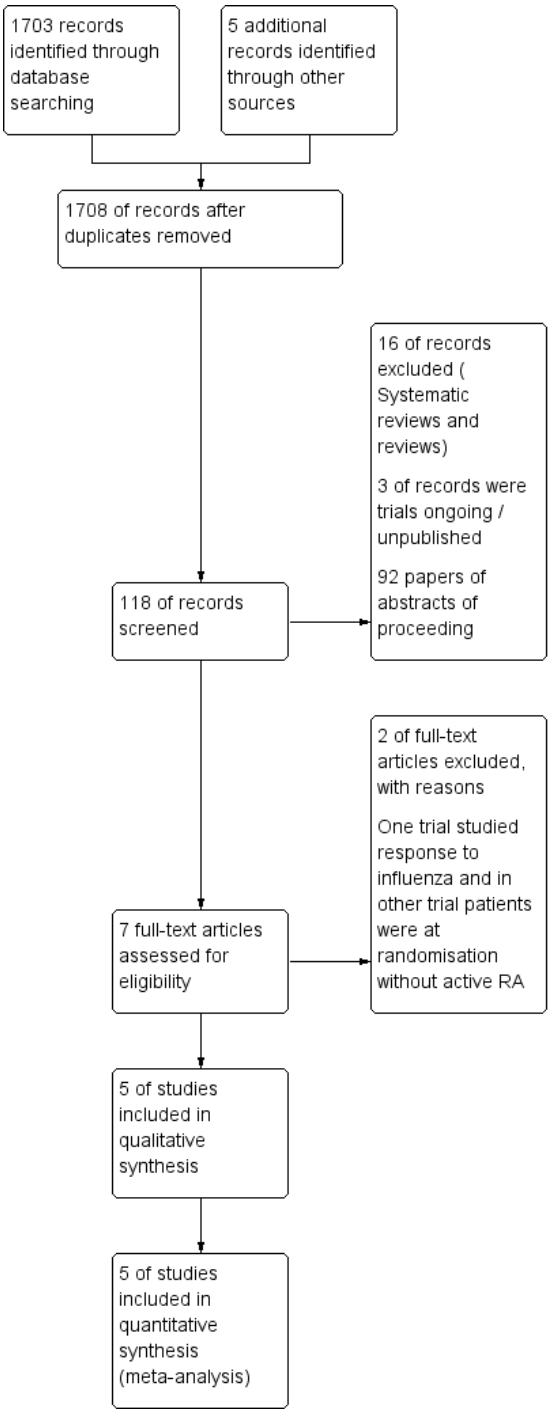
RESULTS

Description of studies

Results of the search

See the flow chart (Figure 1) and 'Results of searches' in Appendix 8.

Figure 1. Study flow diagram.



In this update we found 1703 records identified through database searching on 12 February 2013. Five more trials were identified through other sources. Finally we assessed 118 papers and 7 full-text articles for eligibility. As a result five new trials were included for analysis in this updated review.

According to the Cochrane MECIR standards, CMSG updated the searches on 5 June 2014. However, no more trials were found, only two proceedings of two Japanese trials that we found in clinicaltrials.org, with all of their results. The results, therefore, remained unchanged. The description and the results of this second search are in Appendix 9.

Included studies

In total 11 trials were included: 10 of them involving 4324 people were included in the beneficial assessment (CDP870-004 2001; CDP870-014 2009; CERTAIN 2008; FAST4WARD 2005; NCT00791921 HIKARI; NCT00791999 JRAPID; NCT00993317; RAPID1 2005; RAPID2 2007; REALISTIC 2008) and 10 trials with 3711 people in the assessment of harm (CDP870-014 2009; CERTAIN 2008; Choy 2002; FAST4WARD 2005; NCT00791921 HIKARI; NCT00791999 JRAPID; NCT00993317; RAPID1 2005; RAPID2 2007; REALISTIC 2008). See the Characteristics of included studies and the demographics and flow of patients in Table 1 and Table 2 for details. Only Choy 2002 and CDP870-004 2001 were phase II studies. We found a third phase II study (Kaushik 2005) but we were advised by UCB that: "this publication refers to the 2 previous phase II". All phase III studies were used to assess both benefits and harms. CDP870-004 2001 only contributed data on benefits as it did not report any data on harms. Due to the short follow-up for assessing benefits, Choy 2002 was only included for safety data. The data from the two phase II studies (CDP870-004 2001; Choy 2002) were not pooled with the rest of the studies due to the different follow-ups and doses used.

We retrieved nine phase III trials (CDP870-014 2009; CERTAIN 2008; FAST4WARD 2005; NCT00791921 HIKARI; NCT00791999 JRAPID; NCT00993317; RAPID1 2005; RAPID2 2007; REALISTIC 2008). All trials were funded by UCB. Data from CDP870-014 2009 were provided by UCB from the clinical study summary (www.clinicalstudyresults.org/documents/company-study˙4348˙0.pdf) and the EMEA 2009 reports; they were finally published in 2012 (the study was completed in 2004).

Table 1 shows the demographic and baseline characteristics for the phase III trials: age, gender, rheumatoid factor (RF) positivity, MTX concomitant dose, number of previous DMARDs, basal HAQ and basal DAS28 among other outcomes. Table 2 provides the flow chart of patients in the phase III studies.

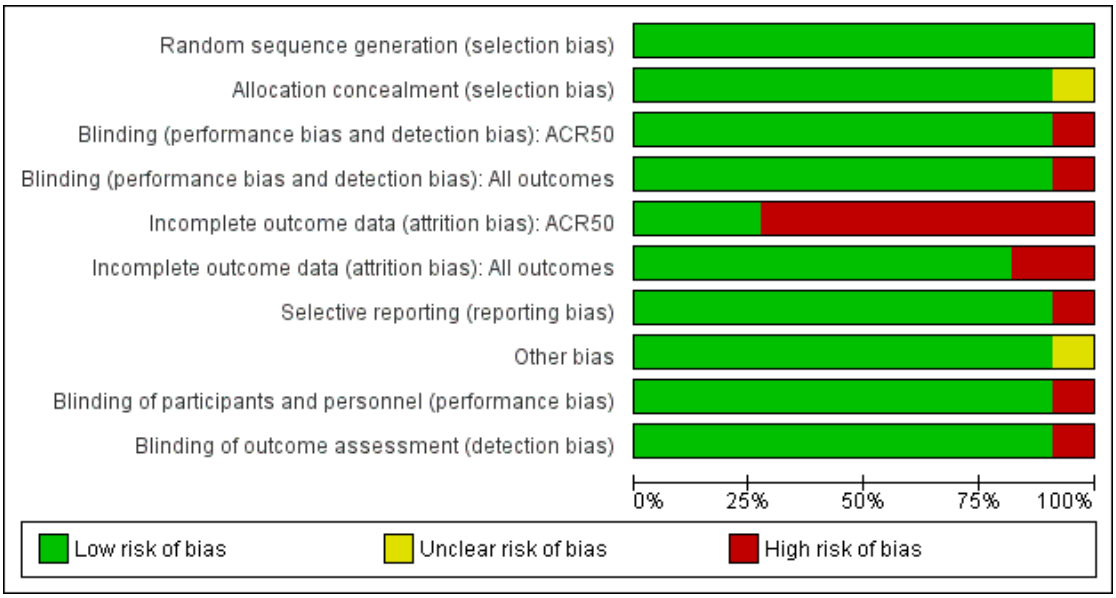
Excluded studies

The main reasons for exclusion were: 1) reviews, 2) different drugs, and 3) another outcome reported. See the table Characteristics of excluded studies.

Risk of bias in included studies

The judgements about each risk of bias item were presented as percentages across all included studies (Figure 2). Most of the trials were rated as low risk of bias. The overall possibility of bias seemed to be low.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



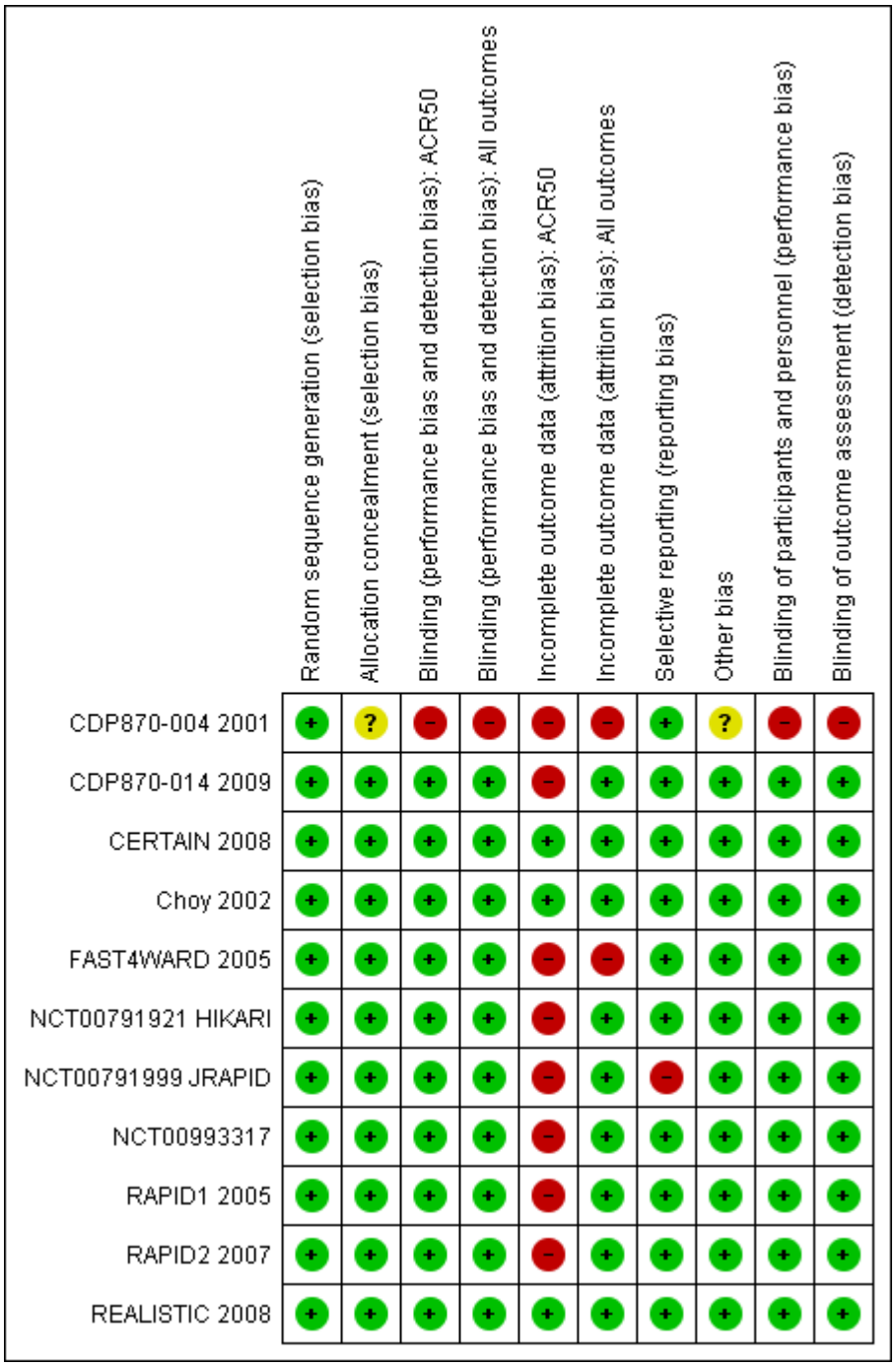
Allocation

All studies but CDP870-004 2001 reported adequate methods of randomisation and allocation concealment. Six studies (CDP870-014 2009; CERTAIN 2008; FAST4WARD 2005; RAPID1 2005; RAPID2 2007; REALISTIC 2008) used the interactive voice response system (IVRS) method of allocation concealment. The Asian trials (NCT00791921 HIKARI; NCT00791999 JRAPID; NCT00993317) were described as: "External central of randomisation. Randomization by blocks"; so the risk of bias seemed to be low.

Blinding

All studies but CDP870-004 2001 reported adequate blinding. Refer to Figure 3.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Phase II:

- CDP870-004 2001 did not disclose the methods of blinding and finally UCB explained to us: "CPD-870 and the placebo utilized in this study (saline) did not have the same viscosity therefore full blinding was not possible. Study drug was to be prepared by a pharmacist having no other involvement in the study; injections of study medications were given by a nurse or physician who had no other involvement in the study...";
- Choy 2002 disclosed the methods of blinding: "Placebo (sodium acetate buffer) was given similarly as a single intravenous infusion of 100 ml over 60 min". It was unlikely that the blinding could have been broken. UCB explained to us: "all data were entered and Database locked after completion of the clinical phase for the first study period and before ESR and CRP were entered into the database. ESR and CRP data were withheld from investigator and sponsor study personal during the course of the study because knowledge of patient's profile could potentially unblind the study..., auto AB, anti CZP level, TNFalpha, IL6 and IL1b were transferred into the database after Database lock."

Phase III:

- UCB told us, "in FAST4WARD 2005, CDP870-014 2009, RAPID1 2005, RAPID2 2007, CERTAIN 2008, REALISTIC 2008, all the study staff with the exception of the unblinded dispenser, was blind to the treatment. Each study center was required to have a written blinding plan in place signed by the Principal Investigator, which detailed the study center's steps for ensuring that the double blind nature of the study was maintained. All the studies were monitored by two different independent teams from the sponsor, one devoted to blind data and one devoted to possibly unblinded information (such as study medications related topics) and completely separate documentation/filing systems were maintained for the duration of the trials";
- RAPID1 2005, "Radiographs were read at a central location by 3 independent readers. Readers were blinded as to the patient's identity, clinical data, treatment, and time point (sequence) at which the radiograph was taken";
- RAPID2 2007, "Radiographs were read centrally and blinded (for treatment, visit and patient identification) and independently by two experienced readers";
- FAST4WARD 2005 disclosed methods of blinding, "Solutions of active drug or placebo were prepared by the pharmacist or other unblinded, qualified site personnel, before distributing to blinded study personnel for administration".
- in the Japanese and Korean trials (NCT00791921 HIKARI; NCT00791999 JRAPID; NCT00993317) "All study staff with the exception of the unblinded dispenser were blind to the treatment, ... These unblinded personnel were not allowed to engage in any other study activities".

For these reasons we rated the risk of bias for blinding as low.

Incomplete outcome data

All studies except the small phase II trial (CDP870-004 2001) reported adequate methods of handling missing outcome data. All other studies had a full account of all withdrawals and reasons for withdrawals. Where possible, we extracted data to allow an intention-to-treat analysis in CDP870-014 2009; FAST4WARD 2005; NCT00993317. We considered a less than 80% completion rate in the treatment group as a high risk of bias; 8 out of 11 studies reported less than 80% completion rates.

The completion rates in the certolizumab pegol group ranged from 68% in FAST4WARD 2005 to 90% in REALISTIC 2008. In all trials, fewer patients in the placebo-treated group completed the trial compared to the treatment arm. More patients who were treated with placebo withdrew due to lack of efficacy. The percentage of those completing the trial in the placebo group ranged from 15% in the 12-month results of NCT00791921 HIKARI to 86% in the 12-weeks results of REALISTIC 2008. Missing data were imputed using last observation carried forward in most trials. The risk of bias appeared to be high. Refer to Figure 3.

Selective reporting

All studies showed planned outcomes, except NCT00791999 JRAPID. Finally ACR20/50/70 was reported by UCB as a figure as well as providing the DAS, but we could not pool DAS data and we had no information about the modified Total Sharp Score (mTTS) for radiographic progression.

We changed the assessment of the bias in FAST4WARD 2005 because all the primary outcomes were described in the paper.

In our previous systematic review the trial CDP870-014 2009 only reported ACR20, but the ACR50, HAQ disability index and acute phase reactant (CRP) are now available so we have changed our likelihood of bias assessment to low.

In summary, we think the risk of reporting bias in this update is low. Refer to Figure 3.

Other potential sources of bias

We did not detect potential threats to validity, such as fraud or imbalance in the groups (relating to the baseline characteristics). All studies included in this review were sponsored by the manufacturer of certolizumab pegol. There is evidence that industry-sponsored trials may overestimate the treatment effect (Bhandari 2004) and there is also evidence that most of the authors of published trials have a conflict of interest. However, there is a lack of

consensus on whether these conflicts result in reduced quality of the trials and, in view of this, we have decided to rate the risk of bias of this domain as low.

We searched for more trials as well as for more information regarding those trials that we had found as unpublished trials during the search (see Characteristics of ongoing studies table), but no information was available either from the sponsors or from any publication. UCB explained to us that the papers for these trials have been accepted and are expected to be published.

In summary, we think the risk of other potential sources of bias is low in this update. Refer to Figure 3.

Summary assessment of risk of bias by outcomes

Figure 2 and Figure 3 provide a graphical summary of the results of the risk of bias assessments for the 11 included studies.

The main major outcomes

ACR 50 response at six months: the five studies included in the meta-analysis were rated well in terms of adequate allocation concealment, blinding and reporting of appropriate outcomes. However, there was a concern about bias in terms of incomplete outcome data due to the high dropout rates in four of the five studies. Another concern was that all studies were sponsored by the manufacturer of certolizumab pegol.

HAQ change from baseline, response at six months: the four studies included in the meta-analysis were rated well in terms of adequate allocation concealment, blinding and reporting of appropriate outcomes. However, there was a concern about bias in terms of incomplete outcome data due to the high dropout rates in three of the four studies. Another concern was that all studies were sponsored by the manufacturer of certolizumab pegol.

Serious adverse events with certolizumab pegol 200 mg at any time of follow-up: the seven studies included in the meta-analysis were rated well in terms of adequate allocation concealment, blinding and reporting of appropriate outcomes. All of them were analysed with ITT for all randomised patients who received at least one dose, but in two out of seven studies the analysis was per protocol: in RAPID2 2007 "two patients in the placebo group received certolizumab pegol 200 mg and were included in the certolizumab pegol 200 mg group for safety evaluations", and in REALISTIC 2008 nine patients less were analysed in the certolizumab pegol arm and three patients less in the placebo group. Another concern was that all studies were sponsored by the manufacturer of certolizumab pegol.

Effects of interventions

See: **Summary of findings for the main comparison** Certolizumab pegol 200 mg sc (with or without MTX) versus placebo (with or without MTX) for rheumatoid arthritis in adults

The analysis was performed depending on the drug exposure time for subcutaneous (sc) doses of 200 mg and 400 mg, the doses used in the trials. For 400 mg the most common was at four-week intervals and for 200 mg sc the most frequently used was every other week, but in some trials like RAPID1 and RAPID2 the interval was every two weeks for the 400 mg dose as well. As we had two periods of follow-up (six months and one year) in one study, we could not pool them thus we pooled each outcome at each follow-up. Moreover, we had studies with more than one dose so we split the placebo arm to obtain pooled results. We did not find strong differences that could justify not combining the results for benefits and harms. We decided to perform a random-effects model in spite of the low values of I^2. Although it was the same drug, there is clear clinical heterogeneity (different doses, allowing MTX or not, different follow-up, different duration of RA, etc.).

Major outcomes

ACR50

Significant improvements were observed for all doses at any given time for the ACR50 compared to placebo (see 'Benefits' tables, ACR Table 3, Data and analyses).

The ACR50 with 200 mg certolizumab pegol showed, at 24 weeks, a RR of 3.80 (95% CI 2.42 to 5.95), 5 out of 10 studies, involving 1445 patients (Analysis 2.2); and at 52 weeks a RR of 5.03 (95% CI 3.04 to 8.32), 1 out of 10 studies, involving 592 patients (Analysis 5.2).

The ACR50 with 400 mg certolizumab pegol showed, at 24 weeks, a RR of 4.65 (95% CI 3.09 to 6.99), 5 out of 10 studies, involving 1591 patients (Analysis 3.2). The ACR50 with 400 mg certolizumab pegol showed, at 52 weeks, a RR of 5.27 (95% CI 3.19 to 8.71), 1 out of 10 studies, involving 589 patients (Analysis 6.2).

The NNT was close to 4 for all the subanalyses (Table 3).

Health-related quality of life

An improvement in physical function and quality of life measured as the HAQ and SF-36 (in the mental and physical components) at all times of follow-up (see 'Health-related quality of life' tables, Table 4) was seen with certolizumab pegol compared to placebo.

HAQ, 24 weeks, 200 mg: MD -0.35 (95% CI -0.43 to -0.26), 4 out of 10 studies, involving 1268 patients (Analysis 11.1); HAQ, 24 weeks, 400 mg: MD -0.38 (95% CI -0.48 to -0.28), 4 out of 10 studies, involving 1425 patients (Analysis 11.2).

HAQ disability index (HAQ-DI), 24 weeks, any dose: MD -0.36 (95% CI -0.43 to -0.29), 5 out of 10 studies, involving 2246 patients (Analysis 12.1); HAQ-Di, 52 weeks, any dose: MD -0.43 (95% CI -0.52 to -0.35), 1 out of 10 studies, involving 982 patients (Analysis 13.1).

SF-36 physical component summary (PCS), 24 weeks, any dose: MD 5.29 (95% CI 4.37 to 6.21), 3 out of 10 studies, involving 1765 patients (Analysis 18.1); SF-36 PCS, 52 weeks, any dose: MD 6.47 (95% CI 5.13 to 7.81), 1 out of 10 studies, involving 982 patients (Analysis 20.1).
SF-36 mental component summary (MCS), 24 weeks, any dose: MD 4.01 (95% CI 2.94 to 5.08), 4 out of 10 studies, involving 2012 patients (Analysis 19.1); SF-36 MCS, 52 weeks, any dose: MD 4.30 (95% CI 2.57 to 6.03), 1 out of 10 studies, involving 982 patients (Analysis 21.1).

DAS-28

Significant improvements were observed for all doses and at any given time compared to placebo.
The RR for patients achieving remission (DAS < 2.6) with 100 mg certolizumab pegol at 24 weeks was 2.82 (95% CI 1.6 to 5), 1 out of 10 studies, involving 1063 patients (Analysis 25.1).
The proportion of patients achieving remission (< 2.6) was higher in the 200 mg certolizumab pegol group than in the placebo group (RR 8.47, 95% CI 4.15 to 17.28) at 24 weeks, 4 out of 10 studies, involving 1381 patients (Analysis 25.2); and RR of 10.36 (95% CI 3.29 to 32.58) at 52 weeks, 1 out of 10 studies, involving 587 patients (Analysis 25.4).
The RR for patients achieving remission (< 2.6) with 400 mg certolizumab pegol was 7.18 (95% CI 3.12 to 16.50) at 24 weeks, 3 out of 10 studies, involving 1201 patients (Analysis 25.3); and at 52 weeks the RR was 12.49 (95% CI 3.99 to 39.12), 1 out of 10 studies, involving 583 patients (Analysis 25.5).

Radiological changes

Radiological changes were expressed as modified Total Sharp Scores (mTSS), the erosion score (ES) and joint space narrowing (JSN). All certolizumab pegol groups showed improvements compared to placebo in the mean changes from baseline. There was a clear radiological benefit, regardless of the dose, that was associated with drug exposure time (see 'Radiological changes', Table 5).
Erosion score (ES), 200 mg, 24 weeks: MD -0.67 (95% CI -0.96 to -0.38), 2 out of 10 studies, involving 859 patients (Analysis 33.1).
Erosion score (ES), any dose, 24 weeks: MD -0.70 (95% CI -0.98 to -0.42), 2 out of 10 studies, involving 1437 patients (Analysis 34.1).
Erosion score (ES), any dose, 52 weeks: MD -1.45 (95% CI -2.11 to -0.79), 1 out of 10 studies, involving 908 patients (Analysis 35.1).
Joint space narrowing (JSN), any dose, 24 weeks: MD -0.50 (95% CI -0.79 to -0.21), 2 out of 10 studies, involving 1439 patients (Analysis 37.1).
Joint space narrowing (JSN), any dose, 52 weeks: MD -1.10 (95% CI -1.88 to -0.33), 1 out of 10 studies, involving 911 patients (Analysis 38.1).
Modified Total Sharp Scores (mTSS), any dose, 24 weeks: MD -1.18 (95% CI -1.67 to -0.69), 2 out of 10 studies, involving 1437 patients (Analysis 39.1).
Modified Total Sharp Scores (mTSS), any dose, 52 weeks: MD -2.50 (95% CI -3.70 to -1.30), 1 out of 10 studies, involving 908 patients (Analysis 40.1).

Serious adverse events (SAEs) as defined in the studies

The clinical study summary of CDP870-004 2001 did not define SAEs. All the new trials that were added in this update reported on SAEs.
We reported adverse events depending on the doses:
SAE for certolizumab pegol 200 mg and any follow-up Peto OR 1.77 (95% CI 1.27 to 2.46), 7 out of 9 studies, involving 2729 patients (Analysis 8.6);
SAE for certolizumab pegol 400 mg and any follow-up Peto OR 1.98 (95% CI 1.36 to 2.90), 5 out of 9 studies, involving 1584 patients (Analysis 9.7); 240 events were reported in the certolizumab pegol groups versus 69 events in the control groups.

All withdrawals

There were more withdrawals "at any dose and at any follow-up" in placebo groups (56%) versus the certolizumab pegol groups (23%) (Analysis 48.1).
There were more withdrawals "due to lack of efficacy" in placebo groups (61%) versus the certolizumab pegol groups (19%) (Analysis 48.2).
Withdrawals at any dose and at any follow-up: RR 0.42 (95% CI 0.36 to 0.50), 10 out of 10 studies, involving 3962 patients (Analysis 48.1).
Withdrawals at any dose and at any follow-up due to lack of efficacy: RR 0.30 (95% CI 0.25 to 0.37), 5 out of 10 studies, involving 2195 patients (Analysis 48.2).

Withdrawals due to adverse events

There were more withdrawals "at any dose and at any follow-up due to adverse events" in the certolizumab pegol groups (5%) versus placebo groups (3%).
Withdrawals at any dose and at any follow-up due to adverse events: Peto OR 1.66 (95% CI 1.15 to 2.37), 9 out of 10 studies, involving 3998 patients (Analysis 48.3).
We have included all results in Summary of findings for the main comparison.

Minor outcomes

ACR20 and ACR70

We saw an improvement in ACR20 and ACR70 compared to placebo for all doses and at any time.
ACR20 for any dose at 24 weeks: RR 2.76 (95% CI 2.29 to 3.33), 8 out of 10 studies, involving 2935 patients (Analysis 4.1); ACR20 for any dose at 52 weeks: RR 2.06 (95% CI 1.61 to 2.62), 1 out of 10 studies, involving 982 patients (Analysis 7.1).
ACR70 for any dose at 24 weeks: RR 4.15 (95% CI 2.68 to 6.42), 7 out of 10 studies, involving 2705 patients (Analysis 4.3); ACR70 for any dose at 52 weeks: RR 3.14 (95% CI 1.86 to 5.29), 1 out of 10 studies, involving 982 patients (Analysis 7.3).

Adverse events

We reported all adverse events in Data and analyses but not all of them were commented on in the present section, only those that we thought were the most interesting (see Table 6).

Any adverse event

We pooled the data for any adverse event from nine trials: 200 mg certolizumab pegol RR 1.18 (95% CI 1.10 to 1.27), 7 out of 9 studies, involving 2739 patients (Analysis 8.1); and 400 mg certolizumab pegol RR 1.21 (95% CI 1.11 to 1.31), 5 out of 9 studies, involving 1584 patients (Analysis 9.1).
We excluded Choy's study because it showed more events than patients in the certolizumab pegol group (62 events in 24 patients) as well as in the placebo group (19 events in 12 patients). Thus the RR could not be estimated.

Adverse events: severe intensity as defined in the studies

There were no differences in the number of SAEs between patients treated with 200 mg (Peto OR 1.14, 95% CI 0.78 to 1.65), 4 out of 9 studies, involving 2249 patients; and patients treated with 400 mg of certolizumab pegol (Peto OR 1.23, 95% CI 0.83 to 1.81), 4 out of 9 studies involving 1422 patients. See more details in Analysis 8.4; Analysis 9.4.

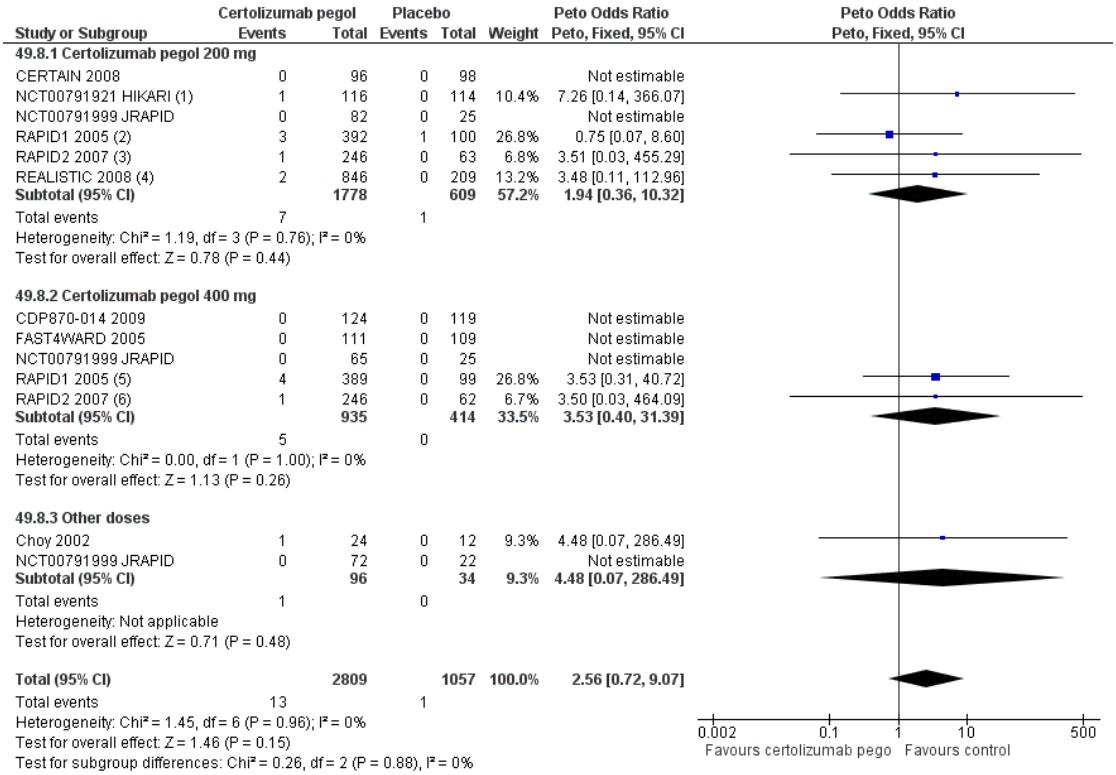
Adverse events leading to death as defined in the studies

We did not find statistically significant differences in the number of adverse events leading to death between the placebo and certolizumab pegol-treated groups. Eleven deaths due to adverse events in the certolizumab pegol groups were reported versus one death in the control groups: 200 mg certolizumab pegol Peto OR 2.34 (95% CI 0.46 to 11.84), 5 out of 9 studies involving 2443 patients (Analysis 8.8); 400 mg certolizumab pegol Peto OR 2.16 (95% CI 0.40 to 11.79), 3 out of 9 studies, involving 1179 patients (Analysis 9.8).

Death

In RAPID1 2005, in the placebo-treated group one patient died of myocardial infarction. In the 200 mg certolizumab pegol-treated group one patient died of hepatic neoplasm, another died of peritonitis and cirrhosis, and one died during the post-treatment period (> 84 days after the last injection). In the 400 mg certolizumab pegol-treated group one died of cerebral stroke, one of myocardial necrosis, one of cardiac arrest and one of atrial fibrillation.
In RAPID2 2007, in the 200 mg certolizumab pegol-treated group one patient died of myocardial infarction; one patient died during the study in the 400 mg certolizumab pegol-treated group (fracture, shock), which was assessed as unlikely to be related to the study medication.
In Choy 2002, in the open phase one patient in the certolizumab pegol-treated group (20 mg/kg CDP870) died from complications following rapid drainage of a large, chronic rheumatoid pericardial effusion. In the opinion of the investigator this event was unrelated to treatment with CDP870.
In REALISTIC 2008, one patient died of sigmoid diverticulitis and one of necrotizing pneumonia; both deaths were ruled out as possibly related to certolizumab pegol.
In NCT00791921 HIKARI, one patient died of a rupture of a dissecting aortic aneurysm in the thoracic region, but UCB considered that unlikely to have been related to the study medication.
CDP870-014 2009; CERTAIN 2008; FAST4WARD 2005; NCT00791999 JRAPID did not report any deaths.
Overall certolizumab pegol deaths: Peto OR 2.56 (95% CI 0.72 to 9.07), 9 out of 9 studies, involving 3866 patients (Analysis 49.8; Figure 4).

Figure 4. Forest plot of comparison: 49 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), outcome: 49.8 Deaths.



Serious adverse infections (SAI)

This composite outcome included any severe events of infections, infestations and tuberculous (disseminated tuberculosis, peritoneal tuberculosis, pulmonary tuberculosis, lymph node tuberculosis, tuberculosis), lower respiratory tract infection, and obstructive chronic bronchitis with acute exacerbation. More SAIs were reported in the 200 mg certolizumab pegol-treated group (Peto OR 3.30, 95% CI 1.45 to 7.51), 2 out of 9 studies, involving 964 patients; and in the 400 mg certolizumab pegol-treated group (Peto OR 3.25, 95% CI 1.65 to 6.39), 4 out of 9 studies, involving 1422 patients; 58 events were reported in the certolizumab pegol groups versus six events in the control groups. There were no differences between the rates of SAIs in the 200 mg and 400 mg certolizumab pegol groups. See more details in Analysis 8.7; Analysis 9.6.

Tuberculosis

A significant increase in the number of cases of tuberculosis was observed in both of the certolizumab pegol-treated groups: seven patients (0.8%) in the certolizumab pegol 200 mg group and five patients (0.7%) in the certolizumab pegol 400 mg group versus no cases in either placebo group: 200 mg certolizumab pegol Peto OR 4.53 (95% CI 0.94 to 21.85), 5 out of 9 studies, involving 2340 patients (Analysis 8.11); 400 mg certolizumab pegol Peto OR 4.55 (95% CI 0.71 to 29.11), 4 out of 9 studies, involving 1364 patients (Analysis 9.13). The overall analysis with both doses (200 and 400 mg) did not reach statistical significance: Peto OR 3.71 (95% CI 0.94 to 14.61), 6 out of 9 studies, involving 3195 patients (Analysis 49.9). In RAPID2 2007, five patients in the certolizumab pegol arms (three in certolizumab pegol 200 mg and two in 400 mg) developed tuberculosis (three from Russia, one each from Poland and Latvia). In NCT00993317 (200 mg

certolizumab pegol) two patients developed tuberculosis.

Other infections

The types of different infections reported (pneumonitis, bacterial arthritis, mastitis, urinary tract infection, herpes viral, bacterial peritonitis, and opportunistic infection) are presented in 'Data and analyses'.

Upper respiratory tract infection was more frequent with 200 mg certolizumab pegol than in the placebo group (Peto OR 1.51, 95% CI 1.08 to 2.09), 7 out of 9 studies, involving 2729 patients (Analysis 8.19); and 400 mg certolizumab pegol (Peto OR 1.42, 95% CI 0.77 2 to 2.61), 4 out of 9 studies, involving 1364 patients (Analysis 9.28).

Nasopharyngitis was more frequent with both doses of certolizumab pegol than in the placebo group: 200 mg certolizumab pegol Peto OR 1.46 (95% CI 1.02 to 2.09) (Analysis 8.23), 6 out of 9 studies, involving 1674 patients; and 400 mg certolizumab pegol Peto OR 1.98 (95% CI 1.26 to 3.11), 4 out of 9 studies, involving 1364 patients (Analysis 9.41). However, neither upper nor lower respiratory tract infections were more frequent compared to placebo with both doses of certolizumab pegol: 200 mg (Peto OR 1.17, 95% CI 0.86 to 1.59), 8 out of 9 studies, involving 3692 patients; and 400 mg (Peto OR 1.66, 95% CI 0.77 to 3.58), 7 out of 9 studies, involving 3073 patients (Analysis 49.10; Analysis 49.11).

Pain

Pain at the site of injection was not statistically significant compared with placebo: in the 200 mg certolizumab pegol-treated group (Peto OR 1.85, 95% CI 0.49 to 6.92), 3 out of 9 studies, involving 1091 patients (Analysis 8.13); and the 400 mg certolizumab pegol-treated group (Peto OR 1.74, 95% CI 0.41 to 7.42), 3 out of 9 studies, involving 1179 patients (Analysis 9.21). The wide CIs were due to the fact that pain was not observed in any placebo group, surprisingly. Similar data were observed for local reactions at the injection site.

Patients' assessment of arthritis pain (visual analogue scale (VAS) score 0 to 100 mm) improved at all doses and at all times. At week 24, the overall mean difference (MD) was -21.07 (95% CI -23.59 to -18.55), 4 out of 9 studies, involving 2064 patients (Analysis 42.1); and at week 52 the MD was -23.48 (95% CI -27.09 to -19.88), 1 out of 9 studies, involving 982 patients (Analysis 43.1).

Other adverse events

Hypertension was more frequent with both doses of certolizumab pegol than with placebo: 200 mg certolizumab pegol Peto OR of 3.09 (95% CI 1.64 to 5.84), 4 out of 9 studies, involving 1353 patients (Analysis 8.24); 400 mg certolizumab pegol Peto OR of 3.35 (95% CI 1.80 to 6.20), 3 out of 9 studies, involving 1121 patients (Analysis 9.32). The secondary events for headache, fever, blood disorders, laboratory disorders, abdominal pain, nasopharyngitis, nausea, urinary tract infections, neck pain, congestive heart failure, pruritus and anaphylaxis are described in detail in Data and analyses.

Despite the report from the EMEA (http://www.ema.europa.eu/docs/en˙GB/document˙library/EPAR˙-˙Public˙assessment˙report/human/001037/WC500069735.pdf), we could not extract more data on adverse events because these data were disclosed as combined data without the number of events in each trial. Moreover, the adverse events were grouped by 'primary system organ class': cardiac disorders, endocrine disorders, neoplasms benign, malignant and unspecified (excluding cysts and polyps).

Assessment of heterogeneity

When we analysed the ACR50 (Analysis 4.2) we found a low probability of statistical heterogeneity (I^2 = 0%). When we reviewed the demographics of phase III studies (Table 1) we found similar proportions of females and males, similar mean ages, and similar baseline HAQ-Di. We only found differences in the mean disease duration in FAST4WARD 2005 and CDP870-014 2009, around 9.4 years compared with around 6 years in most arms of the other studies where data were available (with low heterogeneity, I^2 = 13 %). Disease duration was not available for CERTAIN 2008; NCT00791921 HIKARI; NCT00791999 JRAPID (I^2 = 6%, and an overall I^2 = 7%) (Analysis 50.5). Rheumatoid factor (RF) positivity varied from around 74% in the certolizumab pegol-treated patients in REALISTIC 2008 up to 100% in FAST4WARD 2005. Similarly disease activity measures such as CRP and swollen joint counts, but not DAS-28 and HAQ-D1, were generally lower in REALISTIC 2008.

However, despite these differences there were no compelling reasons for not combining the trial data for the most important variables.

Although 11 trials were included in this update no more than seven trials were analysed in each forest plot, so a funnel plot was not produced.

Subgroup analysis

Subgroup analyses were planned for the duration of the illness (approximately three years evolution), patients' sex, drug dose, administration and methodological quality, but only subgroup analysis regarding the dose of certolizumab pegol was performed. All phase III trials were performed in patients with a high mean duration of RA (from 6.1 to 9.5 years) and we could not obtain any data categorized by sex. All phase III trials allowed previous DMARD treatment (mean from 1.2 to 2 years). All phase III trials included in the meta-analysis were rated as high quality, and so we did not perform more subgroup analysis.

Sensitivity analysis

We have done a sensitivity analysis with the major outcome ACR50. In our previous systematic review we re-analysed quality (adequate sequence generation, good allocation concealment, adequate blinding, etc.) and did not show any changes. In this update we have more information about the quality of the trials from UCB and most trials were rated as high quality trials, so a sensitivity analysis based on quality was not done. However, we sought heterogeneity by analysing for doses of certolizumab pegol, size, use of concomitant MTX, different populations (Japanese and Korean trials versus other populations) and by published versus unpublished trials, but found no statistical heterogeneity (Analysis 50.1; Analysis 50.2; Analysis 50.3; Analysis 50.4; Analysis 50.6).

DISCUSSION

Summary of main results

Certolizumab pegol was FDA approved in 2008 for the treatment of Crohn's disease in adult patients with moderate to severe active disease and who had an inadequate response to conventional therapy. In 2009 the FDA approved certolizumab pegol for adult patients suffering from moderate to severe rheumatoid arthritis.

The drug has been shown to reduce the rate of progression of joint damage, as measured by X-ray, and to improve physical function. Long-term follow-up studies of commercially sponsored RCTs show persistence rates of 88.9% at two years, with 46.7% of patients having low disease activity (Keystone 2012). Whether such rates can be replicated in routine care remains to be seen.

The purpose of this systematic review was to evaluate the benefits and harms of certolizumab pegol for the treatment of people with RA when compared to placebo. We only included RCTs with at least three months of follow-up to assess benefits.

The duration of follow-up was from 12 to 52 weeks and the range of doses of certolizumab pegol varied from 50 to 400 mg given subcutaneously (sc).

Important differences between placebo and certolizumab pegol were observed for measures of disease activity, in favour of certolizumab pegol. The differences were both statistically significant and clinically important for the patient-reported outcomes ACR50, HAQ, and SF-36 (physical (PCS) and mental (MCS) component summary scores), and for structural damage measures. Mean changes in HAQ that are > -0.22 are clinically meaningful, although recent papers show that the cut-off could be higher (-0.37) (Ward 2014). In addition, the results with SF-36 (physical and mental components) can be considered relevant because in patients with RA improvements in the SF-36 PCS and HAQ Disability Index (HAQ-DI) are associated with improved work productivity and reduced long-term disability, healthcare utilization, costs and mortality (Hazes 2010).

All certolizumab pegol groups showed improvements in radiological outcomes compared to placebo, measured as the mean changes from baseline. There was a clear radiological benefit although it should be borne in mind that radiographic changes occur in a relatively small proportion of patients in RA over the duration of research studies.

Serious adverse events were more frequent in the certolizumab pegol groups.

Statistically significant differences were observed in the overall number of withdrawals. Patients in the placebo group were statistically significantly more likely to discontinue treatment, probably due to lack of beneficial effect, but more patients withdrew due to adverse reactions in the certolizumab pegol group. The most frequent side effects were infections, nasopharyngitis and hypertension. Tuberculosis and mortality were increased with certolizumab pegol. These differences did not achieve statistical significance but it should be noted that there was only one death in the placebo group compared with 13 in the certolizumab pegol group. Similarly, there were no cases of tuberculosis in the placebo group. These cases of tuberculosis occurred despite precautions to screen patients for tuberculosis before treatment.

In our previous review we stated we would compare our data with data from the European Medicines Agency (EMEA) documents. We requested access to the drug company submissions to the EMEA for marketing authorisation of certolizumab pegol. Our request was denied despite an appeal. The EMEA stated that "..in the course of emerging legal proceedings before the General Court of the European Union, the Agency has been ordered to suspend the implementation of the certain decisions granting access to documents submitted by marketing authorisation holders of medicinal products".

No new or unexpected adverse events were associated with certolizumab pegol in the long-term analysis of harms. Among the included trials the incidence rate (IR) of deaths was 0.84/100 patients-years (PY) in the certolizumab pegol-treated patients compared to an IR of 0.27/100 PY in the placebo-treated patients. Across all the trials and the open-label extensions, the IR was 0.63/100 PY. Death was primarily related to cardiovascular events (IR 0.18/100 PY) (Bykerk 2013). No data regarding hypertension was disclosed in Bykerk 2013. We observed an increase in the number of patients with hypertension among the certolizumab pegol-treated patients (both 200 and 400 mg of certolizumab pegol). This observation may be relevant to an increased rate of cardiovascular events and deaths with certolizumab pegol. The described deaths appear to be largely due to vascular disease and do not appear to be related to infection or immune suppression. Anti-TNFs have been reported to reduce the risk of cardiovascular events in patients with RA (Dixon 2007).

We found an increased risk of serious infections with certolizumab pegol. This risk is recognised with anti-TNFs, both in randomised trials and observational studies (FDA 2013). We did not find an increased risk of malignancies or lymphoma, neither for 200 mg

nor for 400 mg of certolizumab pegol, as shown in a previous systematic review of anti-TNFs (Lopez Olivo 2012).

Overall completeness and applicability of evidence

We have included all available RCTs for certolizumab pegol in patients with RA, with a June 2014 search date. This updated review provides confirmatory evidence of the benefit of certolizumab pegol for patients with RA.

It is important to state that only one study had a follow-up of 52 weeks. Thus there are important uncertainties about sustained benefits and harms in a disease with a lifelong course and the need for therapy over many years. An additional note of caution relates to the population selection in terms of significant co-morbidities and exclusion of patients with previous malignancy, for example. In all trials except the CERTAIN 2008 trial (without a clear definition of its inclusion and exclusion criteria in clinical trials.org), patients with previous neoplasia, any risk of infectious disease, or previous tuberculosis, or prior treatment with any TNF-alpha inhibitor were excluded. In the NCT00791921 HIKARI; NCT00791999 JRAPID and NCT00993317 trials, patients with New York Heart Association (NYHA) class III or IV heart failure were also excluded. Moreover, in the RAPID1 2005 "Patients who, in the investigator's opinion, were at a high risk of infection were excluded, as were patients who had a history of malignancy, demyelinating disease, blood dyscrasias, or severe, progressive, and/or uncontrolled renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, or cerebral disease". Thus, whilst it is clear that certolizumab pegol is beneficial and has an acceptable safety profile in patients selected for clinical trials, careful clinical judgement is needed to ensure benefits in routine care particularly in patients susceptible to infections such as those patients with chronic respiratory diseases.

Quality of the evidence

The quality of the evidence found in the trials included in this review was high. Studies had high standards for treatment allocation, concealment and blinding, but there may have been a risk of attrition bias. The quality of the evidence was downgraded for all outcomes for this reason. However, other GRADE considerations for downgrading, that is imprecision, indirectness and inconsistency, were rated as 'no', and publication bias was 'undetected'. Despite differences in the importance of the outcomes (higher for ACR50 and DAS remission, and lower for radiological changes) we rated the quality of the evidence as moderate for all the outcomes.

Outcome measures in favour of certolizumab pegol were statistically significant in both random-effects and fixed-effect models. We chose to apply a random-effects model although statistical heterogeneity was low. Clinical heterogeneity, however, was substantial (for example with varying follow-up times, doses, use of methotrexate) and, as expected, pooling resulted in large confidence intervals.

Potential biases in the review process

This updated systematic review has fewer limitations than our earlier review primarily because key data from a greater number of studies, including key study quality data, were available either as published reports or directly from the pharmaceutical company. From 11 included trials, 10 with over 4300 patients reported benefits and 10 trials reported harms, indicating a substantial evidence base. We lacked detail that may have been available in submissions to the EMEA as part of this drug's marketing authorisation and we also did not have access to study protocols, so we were not able to judge whether there was a concern about selective reporting. Lack of availability of detailed study reports with individual patient data denied us the opportunity of presenting a richer description of adverse effects, particularly serious adverse reactions.

Agreements and disagreements with other studies or reviews

The NICE 2009 and EMEA 2009 reports, performed as systematic reviews, have shown results quite similar to those in our review. The beneficial effects (ACR50s) of other anti-TNF agents (golimumab (Singh 2010), infliximab (Blumenauer 2002), etanercept (Chen 2006; Lethaby 2013) and adalimumab (Navarro Sarabia 2005)) are also quite similar to that of certolizumab pegol. The meta-analysis by Singh 2011 described the adverse effects of nine biologics and included randomised controlled trials (RCTs), controlled clinical trials (CCTs) and open-label extensions (OLEs) in any indication (with the exception of HIV/AIDS) showing similar overall results. Moreover, this study found similar results with certolizumab pegol for serious adverse events and serious infections but failed to find an increased rate of withdrawals due to adverse events. In this study the risk of serious infections was about four times higher for certolizumab pegol and the authors performed sensitivity analyses using different models to explain the results. However, the significant differences between certolizumab pegol and five other biologics as determined in the standard dose model (main model) persisted in the unadjusted and dose-adjusted models for each comparison with one minor exception of certolizumab pegol versus golimumab. Indirect comparisons between the biologics suggested some differences in adverse events between drugs. The authors concluded that there is a need for head-to-head trials to verify these differences.

AUTHORS' CONCLUSIONS

Implications for practice

Certolizumab pegol was the first pegylated anti-TNF agent approved by the FDA for the treatment of adult patients with moderate to severe active RA. Our review confirms that the drug is clinically beneficial, including a reduced risk of radiographic damage compared with placebo. Adverse events were more frequent with the active treatment. A potential risk of serious adverse events, hypertension and tuberculosis in susceptible individuals needs to be borne in mind when considering certolizumab pegol or other anti-TNF drugs for active RA.

Implications for research

Treatment options for RA have expanded considerably in recent years and include biologic agents targeting a variety of elements of the inflammatory process. Once efficacy is established it is important that studies focus on comparing agents in clinically relevant populations. New agents continue to be targeted at patients who have failed to respond to methotrexate, yet there are now many established agents available for this population. Therefore, ethics review boards need to consider whether studies which compare agents with placebo or, at best, with background methotrexate and active disease despite this therapy are justifiable. In this situation initial shorter-term studies may be justifiable to establish efficacy, followed by longer-term studies looking at comparative beneficial effects against drugs with known efficacy. Longer-term randomised studies and observational data are clearly important for the assessment of drug toxicity.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

CDP870-004 2001

Methods	Double-blind, multiple dose, 12-week, placebo-controlled dose-ranging study
Participants	326 subjects with a history of inadequate response or intolerance to at least one DMARD and active RA at screening
Interventions	Patients received placebo, 50, 100, 200, 400, 600 and 800 mg sc q4w in two dose groups, panel 1 and panel 2
Outcomes	ACR20, ACR50, ACR70, subset of the ACR criterion, DAS responder rates at week 12 Follow-up 12 weeks
Notes	We only have data from ACR20 at week 12 Funding sources: no data Conflict of interest: no data

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	UCB reported: "Randomized code generated by Pharmaceutical Packaging Service and based on instruction of the randomisation procedure prepared by Celltech R& D statistic"
Allocation concealment (selection bias)	Unclear risk	UCB reported: "Patients were randomly assigned to treatment groups during the DB phase (week 0_12) and received either placebo or CDP-870 SC"
Blinding (performance bias and detection bias) ACR50	High risk	UCB reported as blinded but they explained to us: "CPD-870 and the placebo utilized in this study (saline) did not have the same viscosity therefore full blinding was not possible. Study drug was to be prepared by a pharmacist having no other involvement in the study; injections of study medications were given by a nurse or physician who had no other involvement in the study..."
Blinding (performance bias and detection bias) All outcomes	High risk	See above

CDP870-004 2001 (*Continued*)

Incomplete outcome data (attrition bias) ACR50	High risk	Data were not available
Incomplete outcome data (attrition bias) All outcomes	High risk	Data were not available
Selective reporting (reporting bias)	Low risk	Efficacy was defined as ACR improvement in disease activity at week 12 and was described
Other bias	Unclear risk	There were so few data that was impossible to judge it
Blinding of participants and personnel (performance bias) All outcomes	High risk	See above
Blinding of outcome assessment (detection bias) All outcomes	High risk	See above

CDP870-014 2009

Methods	Randomised double-blind placebo-controlled trial
Participants	Patients with rheumatoid arthritis (RA) who are partial responders to MTX. RA defined by the ACR classification criteria who had received MTX for ≥ 6 months (with at a stable dose of ≥ 15 mg/week) before baseline were included. At inclusion, patients had to have active disease as defined by: Active disease was defined as ≥ 9 tender and 9 swollen joints at screening and at baseline, with either an erythrocyte sedimentation rate (ESR; Westergen) ≥ 30 mm/hour or a C-reactive protein (CRP) level ≥ 15 mg/litre. Other DMARDs had to be discontinued at least 28 days before baseline or five half-lives,whatever longer, prior to first dose of study drug. We do not have more exclusion criteria in the files reported from UCB but probably were similar to another Phase III trial It was a 24 weeks, phase III, double-blind, randomised, multicenter, placebo-controlled study. 250 patients were randomised to one of two regimens of subcutaneous certolizumab pegol 400 mg or placebo sc every 4 weeks for a total of 6 injections. Methotrexate treatment continue during the study taken prior to enrolment in the study. Subjects who completed the current study or who withdrew on or after the Week 12 visit were eligible to participate in the open-label safety study (CDP870-015) The primary objective of this study was to compare the efficacy of certolizumab pegol (CDP870 or CZP) in combination with methotrexate (MTX) to MTX alone in treating the signs and symptoms of subjects with rheumatoid arthritis (RA) who are partial responders to MTX. The study included 250 patients aged over 18 years with RA. Inclusion and exclusion criteria were identical to RAPID1, but were discontinued all DMARD at least 28 days or five half-lives, whatever longer, prior to first dose of study drug. The primary endpoint was ACR20 response at week 24 and safety. Secondary

	efficacy endpoints at week 24 included ACR50, ACR70
Interventions	Certolizumab pegol 400 mg plus MTX or placebo sc plus MTX every 4 weeks for a total of 6 injections
Outcomes	Primary: ACR20 and safety at 24 weeks. Secondary endpoints: Subject's assessment of pain (VAS), Subject's global assessment of arthritis, Physician's global assessment of arthritis, Subject's assessment of physical function by Health Assessment Questionnaire - disability index (HAQ-DI), acute phase reactant value (only CRP for this study) Follow-up 24 weeks
Notes	NCT00544154. Clinical study summary provided by UCB **Funding sources**: UCB **Conflict of interest**: J.V. was a speaker at the meeting organized by UCB and is a member of a UCB advisory board. E.C. has received grants/research support from Abbott Laboratories, Allergan, Boehringer Ingelheim, Chelsea Therapeutics, GSK, Jazz Pharmaceuticals, Merrimack Pharmaceutical, MSD, Pfizer, Pierre Fabre Medicament, Roche, Chugai and Wyeth and UCB Pharma. E.C. has also received consultancy fees from Abbott Laboratories, Allergan, Boehringer Ingelheim, Chelsea Therapeutics, Eli Lilly, GSK, Jazz Pharmaceuticals, Merrimack Pharmaceutical, MSD, Pfizer, Pierre Fabre Medicament, Roche, Schering Plough, Synovate, Chugai, MedImmune and Wyeth and UCB Pharma. E.C. is a member of a Speaker's Bureau for Abbott Laboratories, Allergan, Boehringer Ingelheim, Chelsea Therapeutics, Eli Lilly, GSK, Jazz Pharmaceuticals, Merrimack Pharmaceutical, MSD, Pfizer, Pierre Fabre Medicament, Roche, Schering Plough, Chugai and Wyeth and UCB Pharma. B.V. is a UCB Pharma employee and has been granted UCB Pharma stock appreciation rights. N.G. is a former employee of UCB Pharma, and is currently an employee of Array Biopharma, Inc. N.G. owns UCB Pharma stock. O.D. is an employee of UCB Pharma and holds stock options. R.A. has received research grants from Abbott, BMS, Merck Pharma GmbH, Novartis, Pfizer, Roche and UCB Pharma. R.A. is a member of a speaker's bureau for Abbott Laboratories, BMS, Horizon Pharma, Merck Pharma GmbH, Novartis, Roche, and has received consulting fees from Abbott Laboratories, Horizon Pharma, Merck Pharma GmbH, Novartis and Roche. R.A. has held non-remunerative positions of influence for Abbott Laboratories, BMS, Novartis Pharmaceuticals Corporation and Roche. All other authors have declared no conflicts of interest

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The randomisation code was generated by an independent group following instruction of the randomisation procedures, prepared by the project statistician (EMEA report for the Phase III trial)
Allocation concealment (selection bias)	Low risk	Via Interactive voice recognition system (IVRS)

Blinding (performance bias and detection bias) ACR50	Low risk	UCB explained us that: "All the study staff with the exception of the unblinded dispenser, was blind to the treatment". "Each study center was required to have a written blinding plan in place signed by the principal investigator, which detailed the study center's steps for ensuring that the double blind nature of the study was maintained"
Blinding (performance bias and detection bias) All outcomes	Low risk	See above paragraph
Incomplete outcome data (attrition bias) ACR50	High risk	Full account of all withdrawals and reasons for withdrawals 77.8% of certolizumab pegol group and 53.7% of placebo completed 6 months of treatment. Missing data were imputed for analysis. Judged at high risk of bias due to > 20% dropout rate at 6 months in the treatment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis per protocol for HAQ and safety, quote: "Of the 247 patients randomised, 124 patients in the CZP plus MTX group (98%) and 119 in the placebo plus MTX group (98%) received at least one injection (243 total)"
Selective reporting (reporting bias)	Low risk	All the pre-specified outcomes were studied
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	See above paragraph. "To preserve the blind to clinical research staff, the study site pharmacist labelled clinical supplies (study medication syringes), and a sorbitol placebo was used to match the viscosity of CZP"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above paragraph

CERTAIN 2008

Methods	A phase IIIB, multi-centre, double-blind, placebo-controlled, parallel group study to evaluate the safety and efficacy of certolizumab pegol, administered with DMARD
Participants	Patients with low to moderate disease activity rheumatoid arthritis on DMARDs therapy for at least six months
Interventions	Two 200 mg subcutaneous injections at Week 0, Week 2, and Week 4 followed by 200 mg injections every 2 weeks until the last drug administration (Week 22) versus placebo
Outcomes	Investigation of certolizumab pegol clinical efficacy in achieving clinical remission in patients with moderate to low disease activity rheumatoid arthritis both week 20 and week 24 Follow-up 24 weeks
Notes	http://clinicaltrials.gov/ct2/show/NCT00674362?term=NCT00674362&rank=1 **Funding sources:** UCB **Conflict of interest:** This study is not published. Despite this, paragraph was on the web, "Principal Investigators are **NOT** employed by the organization sponsoring the study"

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Well done
Allocation concealment (selection bias)	Low risk	Allocation by IVRS; so done remotely and therefore concealment satisfactory
Blinding (performance bias and detection bias) ACR50	Low risk	UCB stated: "All the study staff with the exception of the unblinded dispenser, was blind to the treatment. Each study center was required to have a written blinding plan in place signed by the principal investigator, which detailed the study center's steps for ensuring that the double blind nature of the study was maintained"
Blinding (performance bias and detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) ACR50	Low risk	Full account of all withdrawals and reasons for withdrawals 87.5% of certolizumab pegol group and 81% of placebo completed 6 months of treatment. Missing data were imputed for analysis. Judged at high risk of bias due to >

CERTAIN 2008 (*Continued*)

		20% dropout rate at 6 months in the treatment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	85% in SF-36, 84% in Pain VAS, and 94% in HAQ of certolizumab pegol group completed 24 months of treatment. Missing data were imputed for analysis. Judged at high risk of bias due to > 20% dropout rate at 24 months in the treatment group ITT in safety analysis
Selective reporting (reporting bias)	Low risk	All the pre-specified outcomes were studied
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Subject, caregiver, investigator and outcome assessor"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Subject, caregiver, investigator and outcome assessor"

Choy 2002

Methods	Randomised double-blind placebo-controlled trial
Participants	36 patients with rheumatoid arthritis defined by the American College for Rheumatology (ACR) classification criteria. Patients with active diseased defined as having 3 or the following 4 criteria: tender joint count (TJC) $\geq$ 6, swollen joint count (SJC) $\geq$ 3 (based on 28 joint counts), morning stiffness of $\geq$ 45 minutes, and ESR $\geq$ 28 mm/H. Patients had to have failed treatment with at least one DMARD and have been off treatment for at least 4 weeks
Interventions	Ascending-dose group study of a single intravenous infusion of placebo (n = 12) or 1, 5 or 20 mg/kg of certolizumab pegol (each n = 8) for 8 weeks
Outcomes	ACR20, ACR50, ACR70, Pain score (0-10 cm), Disease Activity Score (DAS), TJC, SJC, Health Assessment Questionnaire (HAQ), C-reactive protein (CRP) Follow-up 8 weeks
Notes	This study was only considered to assess safety because follow-up was less than 8 weeks Following the blinded dosing period of 8 weeks, 32 patients received a single open-label infusion of either 5 or 20 mg/kg of certolizumab pegol In the open phase, one patient who received 20 mg/kg died from complications following rapid drainage of a large, chronic rheumatoid pericardial effusion. No infective agent was isolated from either the pericardial fluid or peripheral blood. In the opinion of the

	investigator, this event was unrelated to treatment **Funding sources:** no stated, but UCB had all the data and sent us details of how was done **Conflict of interest:** One author, DA Isenberg, worked for Celltech Research and Development, Slough, UK

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were divided into 4 groups. In each group of 12 patients 8 received active treatment and 4 received placebo. UCB explain to us: "Methods for sequence generation was randomised, DB, sequential ascending dose"
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding (performance bias and detection bias) ACR50	Low risk	The study was blinded and UCB explained to us: "all data were entered and Database locked after completion of the clinical phase for the first study period and before ESR and CRP were entered into the database. ESR and CRP data were withheld from investigator and sponsor study personal during the course of the study because knowledge of patient's profile could potentially unblind the study..., auto AB, anti CZP level, TNFalpha, IL6 and IL1b were transferred into the database after DB lock"
Blinding (performance bias and detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) ACR50	Low risk	Reasons for withdrawals were disclosed 92% of certolizumab pegol group and 50% of placebo completed 8 weeks of treatment. Missing data were imputed for analysis. Judged at high risk of bias due to > 20% dropout rate at 8 weeks in the treatment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Safety analysis was also imputing missing data

Choy 2002 (*Continued*)

Selective reporting (reporting bias)	Low risk	All the outcomes were available in the clinical study report as figures
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	UCB explained to us: " the study pharmacist prepared for infusion the study medication and diluent, the pharmacy covered the solution with an opaque material and labelled it with "130mL CDP870 Engineered Fab' Conjugated to PEG or sodium acetate placebo diluent" "For IV use only", administration details, the patient number, patient initials, date and time to use the medication by and name of investigator."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above

FAST4WARD 2005

Methods	Randomised double-blind trial
Participants	220 patients aged between 18 and 75 years and with RA defined by the ACR classification criteria who had previously failed at least one disease modifying anti-rheumatic drug (DMARD) were included. Patients previously treated with a TNF inhibitor were excluded. Patients had to have a TJC of ≥ 9 (out of 68), SJC of ≥ 9 (out of 66) and one of the following: morning stiffness of ≥ 45 minutes; ESR ≥ 28 mm/H; or CRP > 10 mg/L. Patients with a previous history of a serious or life threatening infection were excluded. Patients with a history of tuberculosis (TB), or evidence of TB on a chest radiograph, or those with a positive reaction to purified protein derivative (PPD) reaction were also excluded. Patients on concurrent corticosteroids were allowed entry provided the dose was the equivalent of 10 mg or less of prednisolone. Parenteral corticosteroids were not permitted
Interventions	Certolizumab pegol 400 mg sc every four weeks (n=111) or placebo (n=109) for 24 weeks
Outcomes	ACR20, 50, 70, HAQ-DI, Pain (VAS) and modified Brief Pain Inventory (mBPI), DAS-28, fatigue, and SF-36 Follow-up 24 weeks
Notes	CPD870 011 **Funding sources:** UCB **Conflict of interest:** JV has received a fee from UCB for speaking at a National Congress; RFvV has received consulting fees from UCB; DB has received

	reimbursement from UCB for attending a symposium and funds for research; JB has received reimbursement from UCB for attending a symposium and funds for research; GC is a full time employee of and holds stocks in UCB; AI is a full time employee at UCB and has shares in the company; NG is a full time employee of UCB and has shares and stock options in the company; VS has worked as an independent biopharmaceutical consultant in clinical development and regulatory affairs since September 1991 and is currently a consultant to various companies, but has not and does not now hold stock in any company. RF has received consulting fees and funds for clinical research from UCB

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Code list prepared by independent group
Allocation concealment (selection bias)	Low risk	Via interactive voice mail response (IVRS)
Blinding (performance bias and detection bias) ACR50	Low risk	UCB stated: "All the study staff with the exception of the unblinded dispenser, was blind to the treatment". "Each study center was required to have a written blinding plan in place signed by the principal investigator, which detailed the study center's steps for ensuring that the double blind nature of the study was maintained"
Blinding (performance bias and detection bias) All outcomes	Low risk	See above paragraph
Incomplete outcome data (attrition bias) ACR50	High risk	68.5% of certolizumab pegol group and 25.7% of placebo completed 6 months of treatment. Missing data were imputed for analysis. Judged at high risk of bias due to > 20% dropout rate at 6 months in the treatment group
Incomplete outcome data (attrition bias) All outcomes	High risk	Full account of all withdrawals and reasons for withdrawals Quote: "All efficacy analyses were performed on the modified intent to treat (mITT) population (all randomised patients who had taken >1 dose of study medication). The actual number of subjects in the summaries varies slightly from the mITT numbers due to non-imputable missing data for each parameter. For the primary analysis, patients were considered "responders" if they achieved an ACR20 response vs baseline at week 24. Patients who withdrew for any reason were considered non responders." The safety analysis was based on the last observation

FAST4WARD 2005 (*Continued*)

		carried forward approach
Selective reporting (reporting bias)	Low risk	All the outcomes were available
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	See above paragraph
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above paragraph

NCT00791921 HIKARI

Methods	Treatment, randomised, double-blind
Participants	Inclusion criteria: • Subjects must have a diagnosis of adult-onset RA of at least 6 months but not longer than 15 years in duration as defined by the 1987 American College of Rheumatology classification criteria • Subjects must have active RA disease as defined by:At least 6 tender joints and 6 swollen jointsESR of 28 mm/hour or CRP of 2.0 mg/dL • Subjects who have failed to respond or have been resistant to at least one DMARD (including MTX) • Subjects in whom MTX cannot be administered for any of the reasons (incomplete response/safety concerns Exclusion criteria: • Patients who have a diagnosis of any other inflammatory arthritisPatients who have a secondary, non-inflammatory type of arthritis (e.g., osteoarthritis, fibromyalgia) • Patients who currently have, or who have a history of, a demyelinating or convulsive disease of the central nervous system (e.g., multiple sclerosis, epilepsy) • Patients who have NYHA (New York Heart Association) Class III or IV congestive heart failure • Patients who currently have, or who have a history of, tuberculosis • Patients who have a high risk of infection (with a current infectious disease, a chronic infectious disease, a history of serious infectious disease) • Patients who currently have, or who have a history of, malignancy • Female patients who are breastfeeding or pregnant, who are of childbearing potential • Patients who previously received treatment with 2 or more anti-TNFα drugs or who previously failed to respond to treatment with 1 or more anti-TNFα drugs Less than 10 % of the patients were exposed to a previous a TNF with a wash-out period of minimum of 3 months for etanercept or 6 months for other biologics
Interventions	Patients received induction doses of 400 mg in weeks 0, 2 and 4 and thereafter 200mg CDP870 given every 2 weeks until week 22 subcutaneously versus placebo

NCT00791921 HIKARI (*Continued*)

Outcomes	Primary outcome ACR20 at week 12; Secondary outcome ACR20 at week 24 Follow-up 24 weeks
Notes	http://clinicaltrials.gov/ct2/show/NCT00791921?term=00791921&rank=1 **Funding sources:** Otsuka Pharmaceutical Co., Ltd. and UCB Japan **Conflict of interest:** This study is already not published. Despite these paragraphs were in the web: "Principal Investigators are **NOT** employed by the organization sponsoring the study. There is **NOT** an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed"

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	External central of randomisation. Randomization by blocks
Allocation concealment (selection bias)	Low risk	The allocation sequence was generate using uniform random numbers from SAS RANUNI function
Blinding (performance bias and detection bias) ACR50	Low risk	"All study staff with the exception of the unblinded dispenser were blind to the treatment, . .. These unblinded personnel were not allowed to engage in any other study activities"
Blinding (performance bias and detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) ACR50	High risk	71% of certolizumab pegol group and 15% of placebo completed 6 months of treatment. Missing data were imputed for analysis. Judged at high risk of bias due to > 20% dropout rate at 6 months in the treatment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full account of all withdrawals and reasons for withdrawals ITT analysis. Quote: "Of the 230 subjects in the Full Analysis Set (FAS), 230 are included in the adverse event reporting based upon the Safety Set (SS) population. The Safety Set includes all subjects randomised who received at least 1 dosing"
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary)

NCT00791921 HIKARI (*Continued*)

		outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Without any details
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above

NCT00791999 JRAPID

Methods	Treatment, randomised, double-blind (subject, caregiver, investigator, outcomes assessor) , dose comparison, parallel assignment, safety/efficacy study
Participants	
Interventions	Drug: CDP870 400mg Drug: CDP870 200mg Drug: CDP870 100mg Drug: placebo of CDP870
Outcomes	Primary outcome measures: ACR20 responder rate (Time Frame: Week 12, 24) (Designated as safety issue: Yes) Secondary outcome measures: ACR20/50/70 responder rate (Time Frame: Week 1, 2, 4, 6, 8, 12, 14, 16, 20, 24) DAS-28 (ESR) (Time Frame: Week 1, 2, 4, 6, 8, 12, 14, 16, 20, 24) Modified Total Sharp Score (Time Frame: Week 24) Follow-up 24 weeks
Notes	http://clinicaltrials.gov/ct2/show/NCT00791999?term=NCT00791999&rank=1 **Funding sources:** Otsuka Pharmaceutical Co., Ltd; UCB Japan Co. Ltd **Conflict of interest:** "Principal Investigators are **NOT** employed by the organization sponsoring the study". "There is **NOT** an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed"

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	External central of randomisation. Randomization by blocks

NCT00791999 JRAPID (*Continued*)

Allocation concealment (selection bias)	Low risk	The allocation sequence was generate using uniform random numbers from SAS RANUNI function
Blinding (performance bias and detection bias) ACR50	Low risk	"All study staff with the exception of the unblinded dispenser were blind to the treatment, ... These unblinded personnel were not allowed to engage in any other study activities"
Blinding (performance bias and detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) ACR50	High risk	66% of certolizumab pegol 100 mg, 80% of certolizumab pegol 200 mg and 76% of certolizumab pegol 400 mg group (overall 74% in certolizumab pegol groups) and 32 % of placebo completed 6 months of treatment. Missing data were imputed for analysis. Judged at high risk of bias due to > 20% dropout rate at 6 months in the treatment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Safety, quote: "Of the 316 subjects in the Full Analysis Set (FAS), 316 are included in the adverse event reporting based upon the Safety Set (SS) population. The Safety Set includes all subjects randomised who received at least 1 dosing"
Selective reporting (reporting bias)	High risk	Subjects were recruited in Japan between 2008 and 2010. In 2008, DAS28 (ESR) and Modified Total Sharp Score were secondary outcomes. In 2012 these outcomes were deleted from http://clinicaltrials.gov/ct2/show/record/NCT00791999?term=NCT00791999&rank=1&sect=X0125
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No details available

NCT00791999 JRAPID (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above

NCT00993317

Methods	Treatment, randomised, double-blind (subject, investigator, outcomes assessor), placebo-controlled, parallel assignment, safety/efficacy study
Participants	Adult-onset RA of at least 6 months but not longer than 15 years in duration as defined by the 1987 ARA criteria, with active disease
Interventions	Drug: CDP870 200mg, 400mg CDP870 given at Week 0, 2, 4 and thereafter 200mg CDP870 given every 2 weeks until week 22 (sc) plus MTX versus placebo plus MTX with the same intervention
Outcomes	ACR20 responder rate Follow-up 24 weeks
Notes	See http://clinicaltrials.gov/ct2/show/study/NCT00993317 **Funding sources:** Korea Otsuka Pharmaceutical Co Ltd **Conflict of interest:** "Principal Investigators are **NOT** employed by the organization sponsoring the study". "There is **NOT** an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed"

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	External central randomisation
Allocation concealment (selection bias)	Low risk	The allocation sequence was generate using uniform random numbers from SAS RANUNI function
Blinding (performance bias and detection bias) ACR50	Low risk	"All study staff with the exception of the unblinded dispenser were blind to the treatment, ... These unblinded personnel were not allowed to engage in any other study activities"
Blinding (performance bias and detection bias) All outcomes	Low risk	See above

NCT00993317 (*Continued*)

Incomplete outcome data (attrition bias) ACR50	High risk	70% of certolizumab pegol group and 50% of placebo completed 6 months of treatment. Missing data were imputed for analysis. Judged at high risk of bias due to > 20% dropout rate at 6 months in the treatment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full account of all withdrawals and reasons for withdrawals Raw data Per protocol analysis in change in (HAQ-DI) 95% of certolizumab pegol group and 95% of placebo were imputed for analysis Safety: ITT Judged at high risk of bias due to > 20% dropout rate at 24 months in the treatment group
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	See above
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above

RAPID1 2005

Methods	Randomised double-blind trial
Participants	982 patients aged over 18 years and with RA defined by the ACR classification criteria who had received MTX for ≥ 6 months (with at a stable dose of ≥ 10 mg/week for at least 2 months) before baseline were included. Patients with a disease duration of >15 years were excluded. Patients previously treated with a TNF inhibitor were also excluded if they had previously failed to respond to treatment. Other DMARDs had to be discontinued at least 28 days before baseline. At inclusion, patients had to have active disease as defined by: Active disease was defined as ≥ 9 tender and 9 swollen joints at screening and at baseline, with either an erythrocyte sedimentation rate (ESR; Westergen) ≥ 30 mm/hour or a C-reactive protein (CRP) level ≥ 15 mg/L

Interventions	982 patients were randomised 2:2:1 to receive treatment with subcutaneous certolizumab pegol at an initial dosage of 400 mg given at weeks 0, 2, and 4, with a subsequent dosage of 200 mg or 400 mg given every 2 weeks, plus MTX, or placebo plus MTX
Outcomes	Co-primary endpoints were the ACR20 at week 24 and the mean change from baseline in the modified Total Sharp Score at week 52. Major secondary end points were: the change from baseline in modified Total Sharp Score at week 24, the change from baseline in the disability Index (DI) of the Health Assessment Questionnaire (HAQ) at weeks 24 and 52, the ACR20 responder rate at week 52, and the ACR50 and ACR70 responder rates at weeks 24 and 52 Follow-up 24-52 weeks
Notes	Patients with a history of tuberculosis or a chest radiograph showing active or latent tuberculosis or those with a positive reaction to purified protein derivative (PPD) reaction were also excluded Funding sources: UCB Conflict of interest: Dr. Keystone has received consulting fees, speaking fees, and/or honoraria from Abbott, Amgen, Wyeth, Centocor, UCB, Roche, Genentech, Schering-Plough, and Bristol-Myers Squibb (less than $10,000 each). Dr. van der Heijde has received consulting fees, speaking fees, and/or honoraria from Abbott, Amgen, Centocor, UCB, Roche, Schering-Plough, and Bristol-Myers Squibb (less than $10,000 each). Dr. Landewe´ has received consulting fees, speaking fees, and/or honoraria from Abbott, Amgen, Bristol-Myers Squibb, Centocor, Schering-Plough, UCB, and Wyeth (less than $10,000 each). Dr. van Vollenhoven has received consulting fees, speaking fees, and/or honoraria from UCB (more than $10,000). Dr. Combe has received consulting fees, speaking fees, and/or honoraria from Abbott, Bristol-Myers Squibb, Merck, Sharp, & Dohme, Roche, Schering, UCB, and Wyeth (less than $10,000 each). Dr. Emery has received consulting fees from UCB (less than $10,000). Dr. Strand receives consulting fees (her primary source of income) from Abbott Immunology, Allergan, Almirall, Al-Pharma, Amgen, AstraZeneca, Bayhill, Bexel, Biogen Idec, Can-Fite, Centocor, Chelsea, Cypress Bioscience, Dianippon Sumitomo, Euro-Diagnostica, FibroGen, Forest, Genelabs, Genentech, Human Genome Sciences, Idera, Incyte, Jazz, Lexicon Genetics Lux Biosciences, Merck Serono, Novartis, Novo Nordisk, Noxxon Pharma, Nuon, Ono Pharmaceutical, Pfizer, Procter & Gamble, Rigel, RiGEN, Roche, Sanofi-Aventis, Savient, Schering-Plough, Scios, SKK, UCB, VLST, Wyeth, XDx, and Zelos Therapeutics (less than $10,000 each) and receives fees as a member of the advisory board for Abbott, Amgen, Biogen Idec, Bioseek, Bristol-Myers Squibb, Can-Fite, Centocor, Chelsea, Cypress, Euro-Diagnostica, Forest, Idera, Incyte, Jazz, Novartis, Pfizer, Rigel, RiGEN, Roche, Savient, Schering-Plough, UCB, XDx, and Wyeth (less than $10,000 each). Dr. Mease has received consulting fees, speaking fees, and/or honoraria from UCB (less than $10,000). Mr. Desai owns stock or stock options in UCB

Risk of bias			***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**	

RAPID1 2005 (*Continued*)

Random sequence generation (selection bias)	Low risk	Code list prepared by independent group
Allocation concealment (selection bias)	Low risk	Interactive voice recognition system (IVRS) used to allocate patient to treatment group (2:2:1 ratio)
Blinding (performance bias and detection bias) ACR50	Low risk	UCB stated: "All the study staff with the exception of the unblinded dispenser, was blind to the treatment. Each study center was required to have a written blinding plan in place signed by the principal investigator, which detailed the study center's steps for ensuring that the double blind nature of the study was maintained"
Blinding (performance bias and detection bias) All outcomes	Low risk	See above paragraph
Incomplete outcome data (attrition bias) ACR50	High risk	65% of certolizumab 200 mg and 70.3% certolizumab 400 mg of group and 22% of placebo completed 12 months of treatment. Missing data were imputed for analysis. Judged at high risk of bias due to > 20% dropout rate at 12 months in the treatment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full account of all withdrawals and reasons for withdrawals HAQ, quote: "Analyses were performed using the last observation carried forward (LOCF) method for imputation of missing scores in the total ITT population and the actual scores (observed) in those who withdrew at week 16" Safety: ITT analysis
Selective reporting (reporting bias)	Low risk	All the outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	See above paragraph
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above paragraph

RAPID2 2007

Methods	Randomised double-blind trial
Participants	619 patients aged over 18 years and with RA of at least 6 months and defined by the ACR classification criteria who had received MTX for ≥ 6 months with at a stable dose of ≥ 10 mg/week for at least 2 months before baseline were included. Patients with a disease duration of > 15 years were excluded. At inclusion, patients had to have active disease as defined by: TJC and SJC of ≥ 9, ESR ≥ 30 mm/H, and a CRP of ≥15 mg/L. Patients previously treated with a TNF inhibitor were also excluded if they had previously failed to respond to treatment
Interventions	Patients were randomised 2:2:1 to one of two regimens of subcutaneous liquid certolizumab pegol (400 mg at weeks 0, 2 and 4, followed by 200 or 400 mg every 2 weeks) plus MTX, or placebo (saline) plus MTX
Outcomes	The primary endpoint was ACR20 response at week 24, and physician's global assessment of disease activity, patient's assessment of pain, Health Assessment Questionnaire-Disability Index (HAQ-DI) and serum CRP or ESR Secondary efficacy endpoints at week 24 included ACR50, ACR70, mean change from baseline in van der Heijde modified Total Sharp Scores (mTSS), Short Form-36 (SF-36) Health Survey,and individual ACR core set variables. Disease activity was assessed using the Disease Activity Score 28-joint assessment 4 (DAS-28 (ESR) Follow-up 24 weeks
Notes	Patients who did not show an ACR20 response at both weeks 12 and 14 were to be withdrawn from the study, designated ACR20 non-responders in the primary analysis and allowed to enter an open-label extension study at week 16 with certolizumab pegol 400 mg every 2 weeks Patients with history of, or positive chest x-ray findings for, tuberculosis, or a positive purified protein derivative (PPD) skin test (defined as positive indurations per local medical practice) were excluded. As per protocol, if a positive PPD skin test was assumed by the local investigators to be related to previous bacille Calmette-Guerin (BCG) vaccination and was not associated with clinical or radiographic suspicion of tuberculosis, patients could be enrolled at the discretion of the investigator. In total, 101 patients (16%) were enrolled with a PPD test > 5 mm at baseline **Funding sources:** UCB **Conflict of interest:** J Smolen, R B Landewé, P Mease, RF van Vollenhoven, A Kavanaugh, M Schiff, GR Burmester, V Strand and D van der Heijde serve as consultants to UCB, Inc. RB Landewé, A Kavanaugh, M Schiff and D van der Heijde receive research funding from UCB, Inc and GR Burmester and J Vencovsky have received honorarium from UCB, Inc for speaking. D Mason and K Luijtens are employees of UCB, Inc. J Brzezicki has nothing to disclose

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Code list prepared by independent group

RAPID2 2007 (*Continued*)

Allocation concealment (selection bias)	Low risk	Interactive voice recognition system (IVRS) used to allocate patient to treatment group (2:2:1 ratio)
Blinding (performance bias and detection bias) ACR50	Low risk	UCB stated: "All the study staff with the exception of the unblinded dispenser, was blind to the treatment. Each study center was required to have a written blinding plan in place signed by the principal investigator, which detailed the study center's steps for ensuring that the double blind nature of the study was maintained"
Blinding (performance bias and detection bias) All outcomes	Low risk	See above paragraph
Incomplete outcome data (attrition bias) ACR50	High risk	71% and 74% of certolizumab pegol 200 mg and certolizumab pegol 400 mg respectively and 13% of placebo completed 6 months of treatment. Missing data were imputed for analysis. Judged at high risk of bias due to > 20% dropout rate at 6 months in the treatment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full account of all withdrawals and reasons for withdrawals Safety: ITT analysis. Quote: "two patients in the placebo group received certolizumab pegol 200 mg and were included in the certolizumab pegol 200 mg group for safety evaluations"
Selective reporting (reporting bias)	Low risk	All the outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	See above paragraph
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Radiographs were read centrally and blinded (for treatment, visit and patient identification) and independently by two experienced readers

REALISTIC 2008

Methods	Treatment, randomised, double-blind (subject, outcomes assessor), parallel assignment, safety/efficacy study
Participants	Patients with established adult patients with moderate-to-severe rheumatoid arthritis
Interventions	400 mg CZP given as two 200 mg subcutaneous (sc) injections at Weeks 0, 2, and 4, followed by 200 mg CZP given as 1 sc injection on Weeks 6, 8, and 10. At Week 12 subjects enter the open-label phase and receive 200 mg of CZP every other week for a minimum 16 additional weeks until CZP is commercially available versus placebo (0.9% saline) given as 2 subcutaneous (sc) injections at Weeks 0, 2, and 4, followed by placebo given as 1 sc injection on Weeks 6, 8, and 10. At Week 12 subjects enter the open-label phase and receive 200 mg of CZP every other week for a minimum 16 additional weeks until CZP is commercially available
Outcomes	To assess the clinical responses rate as measured by ACR20 response rate Week 12. Other outcomes: responder rate, disease activity, fatigue, physical functioning. In the group remaining in the study after week 12: responder rate, disease activity, fatigue, physical functioning. (Time Frame: Week 12 and every 8 weeks thereafter, until study completion) Follow-up 12 weeks
Notes	http://clinicaltrials.gov/ct2/show/results/NCT00717236?term=NCT00717236&rank=1 **Funding sources:** UCB **Conflict of interest:** "Principal Investigators are **NOT** employed by the organization sponsoring the study.". " There **IS** an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed." " Restriction Description: UCB has > 60 but <= 180 days to review results communications prior to public release and may delete information that is confidential and compromises ongoing studies or is considered proprietary. This restriction is not intended to compromise the objective scientific integrity of the manuscript, it being understood that the results shall be published regardless of outcome"

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients were randomised 4:1 via an interactive voice response system"
Allocation concealment (selection bias)	Low risk	"Patients were randomised 4:1 via an interactive voice response system"
Blinding (performance bias and detection bias) ACR50	Low risk	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken. UCB explained us that: "All the study staff with the exception of the unblinded dispenser, was blind to the treatment". "Each study center

REALISTIC 2008 (*Continued*)

		was required to have a written blinding plan in place signed by the principal investigator, which detailed the study center's steps for ensuring that the double blind nature of the study was maintained"
Blinding (performance bias and detection bias) All outcomes	Low risk	See above paragraph
Incomplete outcome data (attrition bias) ACR50	Low risk	90% of certolizumab pegol group and 86% of placebo completed 12 weeks of treatment. Missing data were imputed for analysis. Judged at high risk of bias due to > 20% dropout rate at 12 weeks in the treatment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full account of all withdrawals and reasons for withdrawals ITT analysis for efficacy outcomes but per protocol analysis in safety: 9 patients less in arm of certolizumab pegol and 3 patients less in placebo group
Selective reporting (reporting bias)	Low risk	All the outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Despite blinding is not described, Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken

Choy's study didn't show number of patients in each arm, mean age (SD), percentage of females, previous DMARD, on steroids, on NSAIDs; and DAS was reported as mean change from baseline without SD.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aaltonen 2012	Meta-analysis of randomised controlled trials
Alten 2013	OLE
Andreakos 2003	Different drug/agent studied
Anonymous 2003	Review; different drug/agent studied
Audrey 2010	Meta-analysis of randomised controlled trials
Bain 2003	Different drug/agent studied
Bansback 2005	Different drug/agent studied
Barnes 2007	Review
Baugh 2001	Review
Bayes M 2006	Review
Chang 2006	Different drug/agent studied
Chikanza 2000a	Review in children
Chikanza 2000b	Review
Deeks 2013	Review
Dose Flex 2007	Is a RCT that tested clinical efficacy of two dosing regimes of CZP (200 mg Q2W or 400 mg Q4W + MTX) compared to MTX alone for maintenance of clinical response up to 34 weeks in patients who have achieved ACR20 after a 16 week open-label run-in period of CZP treatment (CZP 200 mg Q2W + MTX). Reason for exclusion is that patients are not with active disease at the moment of randomisation and so is a criterion of out
Evans 2003	Different drug/agent studied
Fanet-Goguet 2004	Review
Fleischmann 2005	Review
Fleischmann 2013	Open-label extension study (OLE)
Gabay 2002	Review
Garber 2005	Different drug/agent studied

(*Continued*)

Genovese 2005	Review
Goldblatt 2005	Review
Graninger 2002	Different drug/agent studied
Ingham 2010	Meta-analysis of randomised controlled trials
Janssen 2012	Meta-analysis of randomised controlled trials
Kathmann 2005	Review
Kaushik 2005	Review
Kavanaugh 2013	Open-label extension study (OLE)
Kavanaugh A	Assessed in RAPID1 and RAPID2, a work productivity survey (WPS-RA)
Keystone 2013	Open-label extension
Keystone 2013a	Open-label extension (OLE)
Kochbati 2004	Review
Launois 2011	Meta-analysis of randomised controlled trials
Launois 2011a	Meta-analysis of randomised controlled trials
Le 2010	Meta-analysis of randomised controlled trials
Le 2012	Meta-analysis of randomised controlled trials
LE Blay P	Meta-analysis of randomised controlled trials
Lopez-Olivo 2012	Meta-analysis of randomised controlled trials
Mealy 2005	Different drug/agent studied
Mok 2004	Review
Moulis 2012	Meta-analysis of randomised controlled trials
Mount 2005	Review
NCT00160641	Just one simple group
NCT00160693	Is an OLE with just one simple group

(*Continued*)

NCT00175877	Just one simple group
NCT00753454	One simple group
NCT00843778	Just one simple group
NCT00993668	Excluded because adverse events were studied in the blinded period just at 4 weeks
Osbourn 2003	Review
Paleolog 2003	Review
Pearce 2001	Review
Pierreisnard 2012	Meta-analysis of randomised controlled trials
Rose-John 2003	Review
Russo 2005	Different drug/agent studied
Sandborn 2003	Crohn's disease review
Schreiber	Crohn's disease
Smolen 2013	Open-label extension (OLE)
Sorbera 2005	Review
Takeuchi 2005	Review
Tanaka 2013	Open-label extension (OLE)
Taylor 2003	Different drug/agent studied
Taylor 2003a	Review
Toussirot 2004	Review
Toussirot 2007	Review
Wang 2013	Meta-analysis of randomised controlled trials
Yamanaka	Conference proceedings without useful data
Yamanaka a	Conference proceedings without useful data
Zhu 2013	Meta-analysis of randomised controlled trials

(*Continued*)

Zwerina 2005	Review

Characteristics of ongoing studies *[ordered by study ID]*

NCT00850343

Trial name or title	Long-term Treatment Study of CDP870 Without Coadministration of MTX in Japanese Rheumatoid Arthritis (RA) Patients
Methods	Randomized, open-label, uncontrolled, parallel assignment
Participants	Japanese RA patients who are transferred from the study (Study 275-08-003), as well as to evaluate the effects of dosing regimens on safety and efficacy of CDP870 in the ACR20 responders who completed Study 275-08-003
Interventions	Drug: CDP870 200mg and CDP870 400mg
Outcomes	Primary outcome: adverse events (Time Frame: At any time) (Designated as safety issue: Yes); Secondary outcome: ACR20/50/70 responder rate DAS-28 (ESR), Modified Total Sharp Score
Starting date	Mar 2009; expected completed date: Mar 2012
Contact information	Drug Information Centeropc_ctr@otsuka.jp
Notes	

NCT00851318

Trial name or title	Long-term Treatment Study of CDP870 as Add-on Medication to MTX in Japanese Rheumatoid Arthritis (RA) Patients
Methods	Randomised, open-label, uncontrolled, parallel assignment, safety/efficacy study
Participants	
Interventions	Two arms: CDP870 200 mg given every 2 weeks, SC; CP870 400mg given every 2 weeks, sc
Outcomes	ACR20/50/70 responder rate (Time Frame: Week 24, 52) ([Designated as safety issue: Yes) DAS28 (ESR) (Time Frame: Week 24, 52) (Designated as safety issue: Yes) Modified Total Sharp Score (Time Frame: Week 24) (Designated as safety issue: Yes)
Starting date	Mar 2009; expected completion Mar 2011
Contact information	Contact: Drug Information Centeropc_ctr@otsuka.jp

NCT00851318 (*Continued*)

Notes	

NCT01451203

Trial name or title	A Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel-group Study to Assess the Efficacy and Safety of CDP870 in Early MTX-naive Rheumatoid Arthritis Patients With Poor Prognosis
Methods	Clinical trial randomised, double-blind
Participants	Estimated enrolment 300
Interventions	400mg of CDP870 given at Week 0, 2. 4, and thereafter 200mg CDP870 given every q2 weeks versus placebo given every q2 weeks
Outcomes	Primary outcome measures:Inhibition of radiographic progression at week 52 Seconary outcomes measures: Inhibition of radiographic progression at week 24 Clinical remission rate at week 24 and week 52
Starting date	October 2011
Contact information	Otsuka Pharmaceutical Co, Ltd
Notes	Final data collection for primary outcomes measure

DATA AND ANALYSES

Comparison 1. Efficacy at 12 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR20	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 certolizumab 50 mg sc	1	47	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.13, 0.57]
1.2 certolizumab 100 mg sc	2	145	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.09, 7.05]
1.3 certolizumab 200 mg sc	5	1577	Risk Ratio (M-H, Random, 95% CI)	1.84 [0.99, 3.40]
1.4 certolizumab 400 mg sc	2	161	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.38, 5.23]
1.5 certolizumab 600 mg sc	1	47	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.51, 0.90]
1.6 certolizumab 800 mg sc	1	46	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.66, 1.04]
2 ACR50	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 certolizumab 50 mg sc	1	47	Risk Ratio (M-H, Random, 95% CI)	1.58 [0.09, 27.88]
2.2 certolizumab 100 mg sc	1	48	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.06, 20.96]
2.3 certolizumab 200 mg sc	3	1239	Risk Ratio (M-H, Random, 95% CI)	2.57 [1.76, 3.75]
2.4 certolizumab 400 mg sc	1	50	Risk Ratio (M-H, Random, 95% CI)	7.33 [0.48, 110.96]
3 ACR70	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 certolizumab 50 mg sc	1	47	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.06, 21.47]
3.2 certolizumab 100 mg sc	1	48	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.03, 14.89]
3.3 certolizumab 200 mg sc	3	1239	Risk Ratio (M-H, Random, 95% CI)	4.52 [2.14, 9.57]
3.4 certolizumab 400 mg sc	1	50	Risk Ratio (M-H, Random, 95% CI)	5.23 [0.34, 80.54]

Comparison 2. Efficacy at 24 weeks, 200 mg certolizumab pegol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 20	6	1675	Risk Ratio (M-H, Random, 95% CI)	3.71 [2.68, 5.13]
2 ACR 50	5	1445	Risk Ratio (M-H, Random, 95% CI)	3.80 [2.42, 5.95]
3 ACR 70	5	1445	Risk Ratio (M-H, Random, 95% CI)	7.26 [3.83, 13.76]

Comparison 3. Efficacy at 24 weeks, 400 mg certolizumab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 20	5	1591	Risk Ratio (M-H, Random, 95% CI)	3.73 [2.43, 5.72]
2 ACR 50	5	1591	Risk Ratio (M-H, Random, 95% CI)	4.65 [3.09, 6.99]
3 ACR 70	5	1591	Risk Ratio (M-H, Random, 95% CI)	7.20 [2.25, 23.03]

Comparison 4. Efficacy at 24 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR20	8	2935	Risk Ratio (M-H, Random, 95% CI)	2.76 [2.29, 3.33]
1.1 certolizumab 100 mg sc	1	98	Risk Ratio (M-H, Random, 95% CI)	2.65 [1.28, 5.47]
1.2 certolizumab 200 mg sc	6	1462	Risk Ratio (M-H, Random, 95% CI)	2.92 [2.17, 3.95]
1.3 certolizumab 400 mg sc	5	1375	Risk Ratio (M-H, Random, 95% CI)	2.65 [1.98, 3.56]
2 ACR50	7	2705	Risk Ratio (M-H, Random, 95% CI)	2.95 [2.37, 3.68]
2.1 certolizumab 100 mg sc	1	98	Risk Ratio (M-H, Random, 95% CI)	2.89 [1.13, 7.38]
2.2 certolizumab 200 mg sc	5	1232	Risk Ratio (M-H, Random, 95% CI)	2.76 [2.02, 3.78]
2.3 certolizumab 400 mg sc	5	1375	Risk Ratio (M-H, Random, 95% CI)	3.18 [2.29, 4.41]
3 ACR70	7	2705	Risk Ratio (M-H, Random, 95% CI)	4.15 [2.68, 6.42]
3.1 certolizumab 100 mg sc	1	98	Risk Ratio (M-H, Random, 95% CI)	6.86 [0.97, 48.72]
3.2 certolizumab 200 mg sc	5	1232	Risk Ratio (M-H, Random, 95% CI)	4.29 [2.36, 7.77]
3.3 certolizumab 400 mg sc	5	1375	Risk Ratio (M-H, Random, 95% CI)	4.04 [1.37, 11.90]

Comparison 5. Efficacy at 52 weeks, 200 mg certolizumab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 20	1	592	Risk Ratio (M-H, Fixed, 95% CI)	4.05 [2.80, 5.87]
2 ACR 50	1	592	Risk Ratio (M-H, Fixed, 95% CI)	5.03 [3.04, 8.32]
3 ACR 70	1	592	Risk Ratio (M-H, Fixed, 95% CI)	6.00 [2.83, 12.74]

Comparison 6. Efficacy at 52 weeks, 400 mg certolizumab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 20	1	589	Risk Ratio (M-H, Fixed, 95% CI)	4.18 [2.89, 6.05]
2 ACR 50	1	589	Risk Ratio (M-H, Fixed, 95% CI)	5.27 [3.19, 8.71]
3 ACR 70	1	589	Risk Ratio (M-H, Fixed, 95% CI)	6.56 [3.10, 13.89]

Comparison 7. Efficacy at 52 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR20	1	982	Risk Ratio (M-H, Random, 95% CI)	2.06 [1.61, 2.62]
1.1 certolizumab 200 mg sc	1	493	Risk Ratio (M-H, Random, 95% CI)	2.04 [1.44, 2.87]
1.2 certolizumab 400 mg sc	1	489	Risk Ratio (M-H, Random, 95% CI)	2.08 [1.48, 2.93]
2 ACR50	1	982	Risk Ratio (M-H, Random, 95% CI)	2.58 [1.83, 3.62]
2.1 certolizumab 200 mg sc	1	493	Risk Ratio (M-H, Random, 95% CI)	2.53 [1.56, 4.10]
2.2 certolizumab 400 mg sc	1	489	Risk Ratio (M-H, Random, 95% CI)	2.62 [1.62, 4.25]
3 ACR70	1	982	Risk Ratio (M-H, Random, 95% CI)	3.14 [1.86, 5.29]
3.1 certolizumab 200 mg sc	1	493	Risk Ratio (M-H, Random, 95% CI)	3.02 [1.44, 6.32]
3.2 certolizumab 400 mg sc	1	489	Risk Ratio (M-H, Random, 95% CI)	3.26 [1.56, 6.82]

Comparison 8. Safety, certolizumab 200 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any adverse event	7	2729	Risk Ratio (M-H, Random, 95% CI)	1.19 [1.07, 1.32]
2 Adverse events Intensity mild	4	2249	Risk Ratio (M-H, Random, 95% CI)	1.18 [1.00, 1.41]
3 Adverse events Intensity moderate	4	2249	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.86, 1.32]
4 Adverse events Intensity severe	4	2249	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.14 [0.78, 1.65]
5 Adverse events related to study drug	2	964	Risk Ratio (M-H, Random, 95% CI)	1.59 [1.27, 1.99]
6 Serious Adverse Events (SAE)	7	2729	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.77 [1.27, 2.46]
7 Serious Infections	2	964	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.30 [1.45, 7.51]
8 Adverse events leading to death	5	2443	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.34 [0.46, 11.84]
9 Adverse events leading to withdrawal	7	2729	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.62 [1.07, 2.44]
10 Death	5	2441	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.56 [0.56, 11.59]
11 Tuberculosis	5	2340	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.53 [0.94, 21.85]
12 Malignancies included lymphoma	6	2570	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.79 [0.29, 2.12]
13 Injection site pain	3	1091	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.85 [0.49, 6.92]
14 Injection side reactions	4	2178	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.28 [1.80, 5.99]
15 Neutralising Anti-certolizumab pegol antibodies	1	373	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.57 [0.71, 29.59]
16 Systemic lupus erythematosus	2	567	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.50 [0.07, 286.06]
17 Prolonged activated partial thromboplastin time (aPTT)	2	500	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.73 [0.98, 7.61]
18 Urinary tract infection	5	2340	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.51, 1.36]
19 Upper respiratory tract infection	7	2729	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.51 [1.08, 2.09]
20 Lower respiratory tract infection/ lung infection	6	2356	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.12 [0.76, 5.95]

21 Headache	5	2372	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.05 [0.67, 1.64]
22 Bacteriuria	1	373	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.30, 3.40]
23 Nasopharyngitis/Pharyngitis	6	1674	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.46 [1.02, 2.09]
24 Hypertension	4	1353	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.09 [1.64, 5.84]
25 Hematuria	1	373	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.36 [0.09, 1.47]
26 Hepatic enzyme increased	2	532	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.49 [0.17, 1.48]
27 AST increased	1	373	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.18 [0.04, 0.86]
28 ALT increased	1	373	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.09 [0.02, 0.45]
29 Back pain	1	591	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.91 [1.11, 7.65]
30 Herpes viral infection	2	821	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.80 [0.34, 100.23]
31 Bacterial peritonitis	1	591	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.52 [0.07, 285.70]
32 Opportunistic infections	4	2070	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.33 [0.46, 117.85]
33 Infections and infestations	7	2712	Risk Ratio (M-H, Random, 95% CI)	1.29 [1.07, 1.56]
34 Gastroenteritis	2	785	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.33, 2.87]
35 Hematologic abnormalities	2	821	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.02 [0.27, 15.21]
36 Decreased haemoglobin	1	591	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.02 [0.09, 11.18]
37 Increased platelet count	1	591	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.05 [0.00, 3.25]
38 Pneumonia	4	1606	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.88 [0.51, 6.99]
39 Diarrhoea	2	321	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.64 [0.22, 1.90]
40 Cerebral haemorrhage including subarachnoid	2	321	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.27 [0.12, 13.50]
41 Nausea/vomiting	2	1249	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.45, 1.50]
42 Acute miocardial infarction	1	194	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
43 Constipation	1	230	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.46 [1.04, 53.63]
44 Skin and subcutaneous tissue disorders	3	516	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.54 [1.81, 6.95]
45 Cough	1	127	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.84 [0.28, 12.22]
46 Pruritus	1	127	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.56 [0.40, 51.56]
47 Abdominal pain/discomfort/dyspepsia	1	127	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.58 [0.80, 8.35]
48 Fatigue	1	127	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.45 [0.18, 11.96]
49 Periodontitis	1	162	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.80 [0.35, 9.16]

Comparison 9. Safety, certolizumab 400 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any adverse events	5	1584	Risk Ratio (M-H, Random, 95% CI)	1.20 [1.06, 1.35]
2 Adverse events Intensity mild	4	1422	Risk Ratio (M-H, Random, 95% CI)	1.25 [1.04, 1.50]
3 Adverse events Intensity moderate	4	1422	Risk Ratio (M-H, Random, 95% CI)	1.24 [1.06, 1.45]
4 Adverse events Intensity severe	4	1422	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.23 [0.83, 1.81]
5 Adverse events related to study drug	3	1179	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [1.19, 1.80]
6 Serious infections	4	1422	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.25 [1.65, 6.39]
7 3Serious Adverse Events (SAE)	5	1584	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.98 [1.36, 2.90]
8 Adverse events leading to death	3	1179	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.16 [0.40, 11.79]

9 Adverse events leading to withdrawal	5	1584	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.01 [1.20, 3.36]
10 Death	4	1422	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.16 [0.40, 11.79]
11 Vomiting	1	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.00, 6.70]
12 Pneumonitis	1	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.00, 6.70]
13 Tuberculosis	3	1179	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.55 [0.71, 29.11]
14 Arthritis bacterial	1	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.26 [0.14, 365.79]
15 Mastitis	1	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.26 [0.14, 365.79]
16 Benign Tumour	1	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.32 [0.46, 117.84]
17 Ischaemeic stroke	1	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.26 [0.14, 365.79]
18 Dizziness postural	1	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.26 [0.14, 365.79]
19 Menorrhagia	1	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.26 [0.14, 365.79]
20 Malignancies included lymphoma	3	1179	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.26 [0.26, 6.08]
21 Injection site pain	3	1179	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.74 [0.41, 7.42]
22 Injection side reactions	5	1584	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.34 [0.20, 0.56]
23 Anti-certolizumab pegol antibodies	2	591	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.70 [2.18, 20.55]
24 Antinuclear antibodies (ANA)	1	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.65 [0.77, 3.53]
25 Prolonged activated partial thromboplastin time (aPTT)	1	371	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.46 [0.80, 7.60]
26 Urinary tract infection	2	959	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.50, 1.52]
27 Back pain	2	831	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.11 [1.48, 6.55]
28 Upper respiratory tract infection	4	1364	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.42 [0.77, 2.61]
29 Lower respiratory tract infection/ lung infection	3	993	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.11 [0.75, 5.95]
30 Headache	4	1364	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.30 [0.76, 2.20]
31 Bacteriuria	1	371	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.75 [0.20, 2.82]
32 Hypertension	3	1121	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.35 [1.80, 6.20]
33 Hematuria	1	371	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.37 [0.09, 1.49]
34 Hepatic enzyme increased	2	533	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.69 [0.25, 1.92]
35 AST increased	1	371	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.58 [0.16, 2.07]
36 ALT increased	1	373	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.67 [0.22, 2.05]
37 Herpes viral infection	1	588	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.53 [0.07, 285.35]
38 Bacterial peritonitis	1	588	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
39 Opportunistic infections	1	588	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
40 Infections and infestations	4	1364	Risk Ratio (M-H, Random, 95% CI)	1.49 [1.11, 1.99]
41 Nasopharyngitis/Pharyngitis	4	1364	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.98 [1.26, 3.11]
42 Gastrointestinal disorders	2	831	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.05 [0.54, 2.03]
43 Hematologic abnormalities	2	750	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.13 [0.21, 6.07]
44 Decreased Haemoglobin	1	588	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.49 [0.03, 9.10]
45 Increased platelet count	1	588	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.02 [0.09, 11.23]
46 Skin and subcutaneous tissue disorders	1	162	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.38 [0.38, 4.94]
47 Acute miocardial infarction	1	162	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.73 [0.13, 340.56]
48 Corneal Perforation	1	162	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.73 [0.13, 340.56]
49 Conjunctivitis allergic	1	162	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.73 [0.13, 340.56]
50 Periodontitis	1	159	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.14, 6.50]
51 Fatigue	1	243	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.46 [0.52, 4.15]

Comparison 10. Mean HAQ-DI from baseline at week 12

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 certolizumab pegol 200 mg sc	1	1063	Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.23, -0.21]

Comparison 11. Mean HAQ-DI from baseline at week 24

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 certolizumab pegol 200 mg sc	4	1268	Mean Difference (IV, Random, 95% CI)	-0.35 [-0.43, -0.26]
2 certolizumab 400 mg sc	4	1425	Mean Difference (IV, Random, 95% CI)	-0.38 [-0.48, -0.28]

Comparison 12. HAQ-DI at 24 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	5	2246	Mean Difference (IV, Random, 95% CI)	-0.36 [-0.43, -0.29]
1.1 certolizumab pegol 200 mg sc	3	985	Mean Difference (IV, Random, 95% CI)	-0.33 [-0.44, -0.23]
1.2 certolizumab pegol 400 mg sc	4	1261	Mean Difference (IV, Random, 95% CI)	-0.38 [-0.48, -0.27]

Comparison 13. HAQ-DI at 52 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	1	982	Mean Difference (IV, Fixed, 95% CI)	-0.43 [-0.52, -0.35]
1.1 certolizumab pegol 200 mg sc	1	493	Mean Difference (IV, Fixed, 95% CI)	-0.42 [-0.54, -0.30]
1.2 certolizumab pegol 400 mg sc	1	489	Mean Difference (IV, Fixed, 95% CI)	-0.45 [-0.57, -0.33]

Comparison 14. SF-36 Physical Component Summary (PCS), week 24

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 certolizumab pegol 200 mg sc	3	1129	Mean Difference (IV, Random, 95% CI)	5.03 [3.90, 6.16]
2 certolizumab pegol 400 mg sc	3	1205	Mean Difference (IV, Random, 95% CI)	5.54 [4.11, 6.97]

Comparison 15. SF-36 Mental Component Summary (MCS), week 24

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 certolizumab pegol 200 mg sc	2	965	Mean Difference (IV, Random, 95% CI)	4.18 [2.70, 5.66]
2 certolizumab pegol 400 mg sc	3	1205	Mean Difference (IV, Random, 95% CI)	4.05 [2.77, 5.34]

Comparison 16. SF-36 Physical Component Summary (PCS), week 52

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 certolizumab 200 mg sc	1	592	Mean Difference (IV, Fixed, 95% CI)	6.06 [4.59, 7.53]
2 certolizumab 400 mg sc	1	589	Mean Difference (IV, Fixed, 95% CI)	6.88 [5.42, 8.34]

Comparison 17. SF-36 Mental Component Summary (MCS), week 52

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 certolizumab pegol 200 mg sc	1	592	Mean Difference (IV, Fixed, 95% CI)	4.3 [2.40, 6.20]
2 certolizumab pegol 400 mg sc	1	589	Mean Difference (IV, Fixed, 95% CI)	4.3 [2.40, 6.20]

Comparison 18. SF-36 Physical Component Summary (PCS) at week 24, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	3	1765	Mean Difference (IV, Random, 95% CI)	5.29 [4.37, 6.21]
1.1 certolizumab pegol 200 mg sc	3	967	Mean Difference (IV, Random, 95% CI)	4.99 [3.79, 6.20]
1.2 certolizumab pegol 400 mg sc	2	798	Mean Difference (IV, Random, 95% CI)	5.62 [3.70, 7.54]

Comparison 19. SF-36 Mental Component Summary (MCS) at week 24, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	4	2012	Mean Difference (IV, Random, 95% CI)	4.01 [2.94, 5.08]
1.1 certolizumab pegol 200 mg sc	3	971	Mean Difference (IV, Random, 95% CI)	4.11 [2.62, 5.61]
1.2 certolizumab pegol 400 mg sc	3	1041	Mean Difference (IV, Random, 95% CI)	3.91 [2.38, 5.44]

Comparison 20. SF-36 Physical Component Summary (PCS) at week 52, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	1	982	Mean Difference (IV, Fixed, 95% CI)	6.47 [5.13, 7.81]
1.1 certolizumab pegol 200 mg sc	1	493	Mean Difference (IV, Fixed, 95% CI)	6.06 [4.17, 7.95]
1.2 certolizumab pegol 400 mg sc	1	489	Mean Difference (IV, Fixed, 95% CI)	6.88 [4.99, 8.77]

Comparison 21. SF-36 Mental Component Summary (MCS) at week 52, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	1	982	Mean Difference (IV, Fixed, 95% CI)	4.3 [2.57, 6.03]
1.1 certolizumab pegol 200 mg sc	1	493	Mean Difference (IV, Fixed, 95% CI)	4.3 [1.86, 6.74]
1.2 certolizumab pegol 400 mg sc	1	489	Mean Difference (IV, Fixed, 95% CI)	4.3 [1.85, 6.75]

Comparison 22. Disease Activity Score (DAS-28) (ESR) remission (< 2.6) at 12 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of patients achieving remission 12 weeks certolizumab 200 mg	1	1063	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.36 [1.53, 3.65]

Comparison 23. Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any dose, 24 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of patients achieving remission 24 weeks	5	2264	Risk Ratio (M-H, Random, 95% CI)	5.28 [3.08, 9.05]
1.1 certolizumab pegol 200 mg sc	4	1222	Risk Ratio (M-H, Random, 95% CI)	5.97 [2.93, 12.17]
1.2 certolizumab pegol 400 mg sc	3	1042	Risk Ratio (M-H, Random, 95% CI)	4.46 [1.95, 10.21]

Comparison 24. Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any dose, 52 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of patients achieving remission 52 weeks	1	977	Risk Ratio (M-H, Fixed, 95% CI)	5.80 [2.60, 12.94]
1.1 certolizumab pegol 200 mg sc	1	491	Risk Ratio (M-H, Fixed, 95% CI)	5.29 [1.69, 16.49]
1.2 certolizumab pegol 400 mg sc	1	486	Risk Ratio (M-H, Fixed, 95% CI)	6.31 [2.03, 19.59]

Comparison 25. Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any time

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of patients achieving remission 12 weeks certolizumab 200 mg	1	1063	Risk Ratio (M-H, Fixed, 95% CI)	2.82 [1.60, 5.00]

2 Proportion of patients achieving remission 24 weeks certolizumab 200 mg	4	1381	Risk Ratio (M-H, Random, 95% CI)	8.47 [4.15, 17.28]
3 Proportion of patients achieving remission 24 weeks certolizumab 400 mg	3	1201	Risk Ratio (M-H, Random, 95% CI)	7.18 [3.12, 16.50]
4 Proportion of patients achieving remission 52 weeks certolizumab 200 mg	1	587	Risk Ratio (M-H, Fixed, 95% CI)	10.36 [3.29, 32.58]
5 Proportion of patients achieving remission 52 weeks certolizumab 400 mg	1	583	Risk Ratio (M-H, Fixed, 95% CI)	12.49 [3.99, 39.12]

Comparison 26. DAS-28 at 12 weeks, 200 mg certolizumab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 DAS 28 (ESR) change from baseline	1	1063	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 27. DAS-28 at 24 weeks, 400 mg certolizumab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 DAS 28 (ESR) change from baseline	2	593	Mean Difference (IV, Random, 95% CI)	-1.46 [-2.49, -0.42]

Comparison 28. DAS-28 at week 52, certolizumab 200 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 DAS 28 (ESR) Change from baseline	1	592	Mean Difference (IV, Fixed, 95% CI)	-0.9 [-1.12, -0.68]

Comparison 29. DAS-28 at week 52, certolizumab 400 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 DAS 28 (ESR) Change from baseline	1	589	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-1.23, -0.77]

Comparison 30. DAS-28 at 24 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	2	839	Mean Difference (IV, Random, 95% CI)	-1.59 [-2.10, -1.08]
1.1 certolizumab pegol 200 mg sc	1	310	Mean Difference (IV, Random, 95% CI)	-1.77 [-2.08, -1.46]
1.2 certolizumab pegol 400 mg sc	2	529	Mean Difference (IV, Random, 95% CI)	-1.45 [-2.49, -0.41]

Comparison 31. DAS-28 at 52 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	1	982	Mean Difference (IV, Fixed, 95% CI)	-0.95 [-1.15, -0.75]
1.1 certolizumab pegol 200 mg sc	1	493	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-1.19, -0.61]
1.2 certolizumab pegol 400 mg sc	1	489	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-1.29, -0.71]

Comparison 32. DAS-28 at 24 weeks, 200 mg certolizumab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 DAS 28 (ESR) change from baseline	1	373	Mean Difference (IV, Fixed, 95% CI)	-1.77 [-2.02, -1.52]

Comparison 33. Erosion score (ES)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from the baseline mean ES at week 24, certolizumab pegol 200 mg	2	859	Std. Mean Difference (IV, Fixed, 95% CI)	-0.35 [-0.50, -0.21]
2 Change from the baseline mean ES at week 24, certolizumab pegol 400 mg	2	869	Mean Difference (IV, Random, 95% CI)	-0.76 [-1.14, -0.37]
3 Change from the baseline mean ES at week 52, certolizumab pegol 200 mg	1	544	Mean Difference (IV, Fixed, 95% CI)	-1.4 [-2.08, -0.72]
4 Change from the baseline mean ES at week 52, certolizumab pegol 400 mg	1	543	Mean Difference (IV, Fixed, 95% CI)	-1.50 [-2.20, -0.80]

Comparison 34. Erosion score (ES) at 24 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	2	1437	Mean Difference (IV, Random, 95% CI)	-0.70 [-0.98, -0.42]
1.1 certolizumab pegol 200 mg sc	2	714	Mean Difference (IV, Random, 95% CI)	-0.67 [-1.06, -0.28]
1.2 certolizumab pegol 400 mg sc	2	723	Mean Difference (IV, Random, 95% CI)	-0.73 [-1.14, -0.32]

Comparison 35. Erosion score (ES) at 52 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	1	908	Mean Difference (IV, Fixed, 95% CI)	-1.45 [-2.11, -0.79]
1.1 certolizumab pegol 200 mg sc	1	455	Mean Difference (IV, Fixed, 95% CI)	-1.4 [-2.32, -0.48]
1.2 certolizumab pegol 400 mg sc	1	453	Mean Difference (IV, Fixed, 95% CI)	-1.5 [-2.44, -0.56]

Comparison 36. Joint space narrowing (JSN)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from the baseline mean JSN 24 weeks, certolizumab pegol 200 mg	2	861	Mean Difference (IV, Random, 95% CI)	-0.45 [-0.77, -0.13]
2 Change from the baseline mean JSN 24 weeks,certolizumab pegol 400 mg	2	869	Mean Difference (IV, Random, 95% CI)	-0.55 [-0.86, -0.24]
3 Change from the baseline mean JSN 52 weeks,certolizumab pegol 200 mg	1	548	Mean Difference (IV, Fixed, 95% CI)	1.00 [-1.85, -0.15]
4 Change from the baseline mean JSN 52 weeks, certolizumab pegol 400 mg	1	544	Mean Difference (IV, Fixed, 95% CI)	-1.2 [-1.98, -0.42]

Comparison 37. Joint space narrowing (JSN) at 24 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	2	1439	Mean Difference (IV, Random, 95% CI)	-0.50 [-0.79, -0.21]
1.1 certolizumab pegol 200 mg sc	2	716	Mean Difference (IV, Random, 95% CI)	-0.46 [-0.87, -0.04]
1.2 certolizumab pegol 400 mg sc	2	723	Mean Difference (IV, Random, 95% CI)	-0.54 [-0.96, -0.13]

Comparison 38. Joint space narrowing (JSN) at 52 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	1	911	Mean Difference (IV, Fixed, 95% CI)	-1.10 [-1.88, -0.33]
1.1 certolizumab pegol 200 mg sc	1	458	Mean Difference (IV, Fixed, 95% CI)	1.00 [-2.11, 0.11]
1.2 certolizumab pegol 400 mg sc	1	453	Mean Difference (IV, Fixed, 95% CI)	-1.2 [-2.27, -0.13]

Comparison 39. Modified Total Sharp Scores (mTSS) at 24 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	2	1437	Mean Difference (IV, Random, 95% CI)	-1.18 [-1.67, -0.69]
1.1 certolizumab pegol 200 mg sc	2	713	Mean Difference (IV, Random, 95% CI)	-1.06 [-1.75, -0.38]
1.2 certolizumab pegol 400 mg sc	2	724	Mean Difference (IV, Random, 95% CI)	-1.30 [-1.99, -0.60]

Comparison 40. Modified Total Sharp Scores (mTSS) at 52 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	1	908	Mean Difference (IV, Fixed, 95% CI)	-2.50 [-3.70, -1.30]
1.1 certolizumab pegol 200 mg sc	1	455	Mean Difference (IV, Fixed, 95% CI)	-2.4 [-4.11, -0.69]
1.2 certolizumab pegol 400 mg sc	1	453	Mean Difference (IV, Fixed, 95% CI)	-2.60 [-4.29, -0.91]

Comparison 41. Patient's assessment of arthritis pain (VAS score 0 to 100 mm)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean change at 24 weeks certolizumab pegol 200 mg	2	965	Mean Difference (IV, Random, 95% CI)	-20.49 [-23.43, -17.55]
2 Mean change at 24 weeks certolizumab pegol 400 mg	3	1182	Mean Difference (IV, Random, 95% CI)	-22.69 [-25.53, -19.84]
3 Mean change at 52 weeks certolizumab pegol 200 mg	1	592	Mean Difference (IV, Fixed, 95% CI)	-22.2 [-26.19, -18.21]
4 Mean change at 52 weeks certolizumab pegol 400 mg	1	589	Mean Difference (IV, Fixed, 95% CI)	-24.7 [-28.62, -20.78]

Comparison 42. Patient's assessment of arthritis pain (VAS score 0 to 100 mm) at 24 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	4	2064	Mean Difference (IV, Random, 95% CI)	-21.07 [-23.59, -18.55]
1.1 certolizumab pegol 200 mg sc	2	803	Mean Difference (IV, Random, 95% CI)	-20.48 [-24.26, -16.69]
1.2 certolizumab pegol 400 mg sc	4	1261	Mean Difference (IV, Random, 95% CI)	-21.35 [-25.08, -17.61]

Comparison 43. Patient's assessment of arthritis pain (VAS score 0 to 100 mm) at 52 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	1	982	Mean Difference (IV, Fixed, 95% CI)	-23.48 [-27.09, -19.88]
1.1 certolizumab pegol 200 mg sc	1	493	Mean Difference (IV, Fixed, 95% CI)	-22.2 [-27.37, -17.03]
1.2 certolizumab pegol 400 mg sc	1	489	Mean Difference (IV, Fixed, 95% CI)	-24.7 [-29.73, -19.67]

Comparison 44. Modified total Sharp scores (mTSS)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from the baseline mean mTSS 24 weeks, certolizumab pegol 200 mg.	2	859	Mean Difference (IV, Random, 95% CI)	-1.06 [-1.58, -0.55]
2 Change from the baseline mean mTSS 24 weeks, certolizumab 400 mg	2	869	Mean Difference (IV, Random, 95% CI)	-1.32 [-1.85, -0.78]
3 Change from the baseline mean mTSS 52 weeks, certolizumab pegol 200 mg	1	545	Mean Difference (IV, Fixed, 95% CI)	-2.4 [-3.68, -1.12]
4 Change from the baseline mean mTSS 52 weeks, certolizumab pegol 400 mg	1	544	Mean Difference (IV, Fixed, 95% CI)	-2.60 [-3.84, -1.36]

Comparison 45. Certolizumab pegol 1mg/kg/day sc

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Headache	1	20	Risk Ratio (M-H, Fixed, 95% CI)	4.5 [0.56, 35.98]
2 Lower respiratory tract infection	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.02, 10.54]
3 Adverse events Intensity severe	1	20	Risk Ratio (M-H, Fixed, 95% CI)	4.33 [0.20, 94.83]
4 Antinuclear antibodies (ANA)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.32, 27.83]
5 Urinary tract infection	1	20	Risk Ratio (M-H, Fixed, 95% CI)	4.33 [0.20, 94.83]

Comparison 46. Certolizumab 5 mg/kg/day sc

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lower respiratory tract infection	1	20	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.11, 20.68]
2 Urinary tract infection	1	20	Risk Ratio (M-H, Fixed, 95% CI)	4.33 [0.20, 94.83]

Comparison 47. Certolizumab 20 mg/kg/day sc

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Headache	1	20	Risk Ratio (M-H, Fixed, 95% CI)	4.5 [0.56, 35.98]
2 Lower respiratory tract infection	1	20	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.32, 27.83]
3 Death	1	20	Risk Ratio (M-H, Fixed, 95% CI)	4.33 [0.20, 94.83]
4 Antinuclear antibodies (ANA)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.11, 20.68]
5 Urinary tract infection	1	20	Risk Ratio (M-H, Fixed, 95% CI)	4.33 [0.20, 94.83]

Comparison 48. Withdrawals

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All Withdrawn: any doses any follow up	10	3962	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.36, 0.50]
2 Withdrawn due to lack of efficacy: any doses any follow up	5	2195	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.25, 0.37]
3 Withdrawals due to adverse events	9	3998	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.66 [1.15, 2.37]

Comparison 49. Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 50 200 mg certolizumab 24 weeks	5	1445	Risk Ratio (M-H, Random, 95% CI)	3.80 [2.42, 5.95]
2 HAQ change from baseline 200 mg certolizumab 24 weeks	4	1268	Mean Difference (IV, Random, 95% CI)	-0.35 [-0.43, -0.26]
3 Serious adverse events certolizumab 200 mg sc	7	2729	Risk Difference (M-H, Fixed, 95% CI)	0.04 [0.02, 0.06]
3.1 certolizumab 200 mg	7	2729	Risk Difference (M-H, Fixed, 95% CI)	0.04 [0.02, 0.06]
4 Proportion of patients achieving remission 24 weeks certolizumab 200 mg	4	1381	Risk Ratio (M-H, Random, 95% CI)	8.47 [4.15, 17.28]
5 Radiological changes: Erosion Scores (ES) certolizumab 200 mg sc	2	859	Mean Difference (IV, Random, 95% CI)	-0.67 [-0.96, -0.38]
5.1 certolizumab 200 mg sc 24 weeks	2	859	Mean Difference (IV, Random, 95% CI)	-0.67 [-0.96, -0.38]
6 All Withdrawals:	10	3962	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.36, 0.50]
7 Withdrawals due to adverse events	9	3998	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.66 [1.15, 2.37]
8 Deaths	9	3866	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.56 [0.72, 9.07]
8.1 Certolizumab pegol 200 mg	6	2387	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.94 [0.36, 10.32]
8.2 Certolizumab pegol 400 mg	5	1349	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.53 [0.40, 31.39]
8.3 Other doses	2	130	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.48 [0.07, 286.49]
9 Tuberculosis	6	3195	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.71 [0.94, 14.61]
9.1 Certolizumab pegol 200 mg	5	2179	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.85 [0.66, 22.30]
9.2 Certolizumab pegol 400 mg	3	1016	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.52 [0.40, 31.33]
10 Upper respiratory tract infections	8	3692	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [0.86, 1.59]
10.1 Certolizumab pegol 200 mg	7	2528	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.28 [0.91, 1.80]
10.2 Certolizumab pegol 400 mg	4	1164	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.81 [0.41, 1.61]
11 Lower respiratory tract infections	7	3073	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.66 [0.77, 3.58]
11.1 Certolizumab pegol 200 mg	6	2218	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.81 [0.62, 5.26]
11.2 Certolizumab pegol 400 mg	3	855	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.52 [0.50, 4.59]
12 Malignancies including lymphoma	7	3749	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.90 [0.39, 2.08]

12.1 Certolizumab pegol 200 mg	6	2570	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.79 [0.29, 2.12]
12.2 Certolizumab pegol 400 mg	3	1179	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.26 [0.26, 6.08]

Comparison 50. Analysis of sensibility ACR50

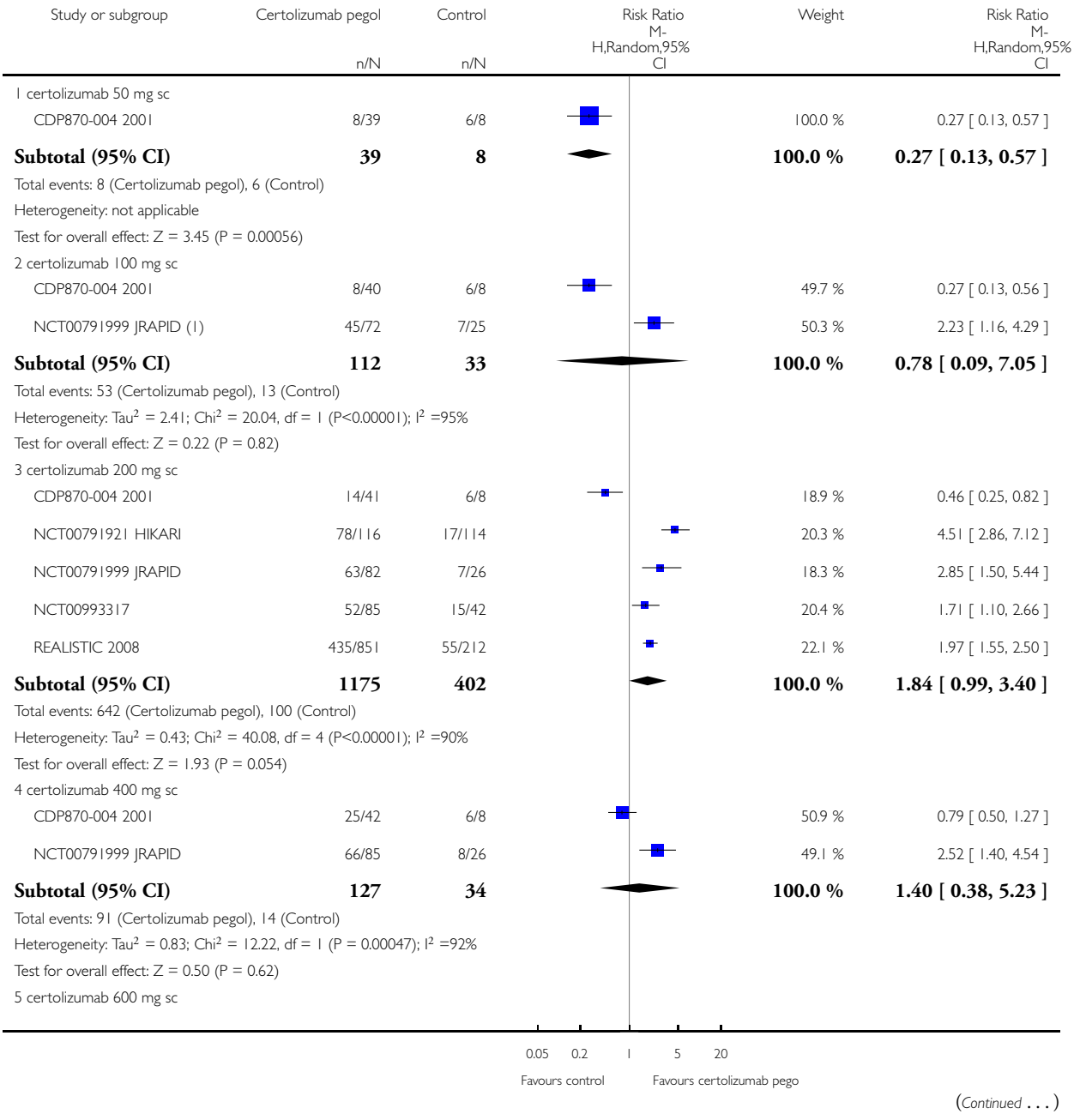
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Doses	8	3768	Risk Ratio (M-H, Random, 95% CI)	2.89 [2.38, 3.51]
1.1 certolizumab 100 mg sc	1	98	Risk Ratio (M-H, Random, 95% CI)	2.89 [1.13, 7.38]
1.2 certolizumab 200 mg sc	6	2295	Risk Ratio (M-H, Random, 95% CI)	2.73 [2.13, 3.51]
1.3 certolizumab 400 mg sc	5	1375	Risk Ratio (M-H, Random, 95% CI)	3.18 [2.29, 4.41]
2 Size	8	3768	Risk Ratio (M-H, Random, 95% CI)	2.89 [2.38, 3.51]
2.1 certolizumab < 200 patients	2	321	Risk Ratio (M-H, Random, 95% CI)	2.44 [1.45, 4.10]
2.2 certolizumab > 200 patients	6	3447	Risk Ratio (M-H, Random, 95% CI)	2.97 [2.41, 3.67]
3 Use of MTX	8	3768	Risk Ratio (M-H, Random, 95% CI)	2.89 [2.38, 3.51]
3.1 With MTX	5	3038	Risk Ratio (M-H, Random, 95% CI)	2.77 [2.21, 3.46]
3.2 Without MTX	3	730	Risk Ratio (M-H, Random, 95% CI)	3.32 [2.23, 4.95]
4 Population	8	3768	Risk Ratio (M-H, Random, 95% CI)	2.89 [2.38, 3.51]
4.1 Asian trials	2	443	Risk Ratio (M-H, Random, 95% CI)	2.66 [1.77, 4.00]
4.2 Other trials	6	3325	Risk Ratio (M-H, Random, 95% CI)	2.96 [2.37, 3.70]
5 Duration of previous disease	6	3258	Risk Ratio (M-H, Random, 95% CI)	2.87 [2.31, 3.57]
5.1 Long previous disease duration (9 years or more)	2	467	Risk Ratio (M-H, Random, 95% CI)	4.02 [2.02, 7.98]
5.2 Short previous disease duration (less than 7 years)	4	2791	Risk Ratio (M-H, Random, 95% CI)	2.75 [2.18, 3.47]
6 Published vs unpublished studies	8	3768	Risk Ratio (M-H, Random, 95% CI)	2.89 [2.38, 3.51]
6.1 Published studies	5	3131	Risk Ratio (M-H, Random, 95% CI)	2.97 [2.36, 3.73]
6.2 Unpublished studies	3	637	Risk Ratio (M-H, Random, 95% CI)	2.71 [1.89, 3.90]

Analysis 1.1. Comparison 1 Efficacy at 12 weeks, any dose, Outcome 1 ACR20.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 1 Efficacy at 12 weeks, any dose

Outcome: 1 ACR20



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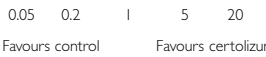
Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
CDP870-004 2001 (2)	25/39	8/8		100.0 %	0.68 [0.51, 0.90]
Subtotal (95% CI)	**39**	**8**		**100.0 %**	**0.68 [0.51, 0.90]**
Total events: 25 (Certolizumab pegol), 8 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.73 (P = 0.0064)					
6 certolizumab 800 mg sc					
CDP870-004 2001 (3)	30/38	8/8		100.0 %	0.83 [0.66, 1.04]
Subtotal (95% CI)	**38**	**8**		**100.0 %**	**0.83 [0.66, 1.04]**
Total events: 30 (Certolizumab pegol), 8 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.61 (P = 0.11)					
Test for subgroup differences: Chi² = 17.21, df = 5 (P = 0.00), I² =71%					



(1) We need to split the results in placebo 22 of 77 patients by 3

(2) From EMEA report, only data for ACR20

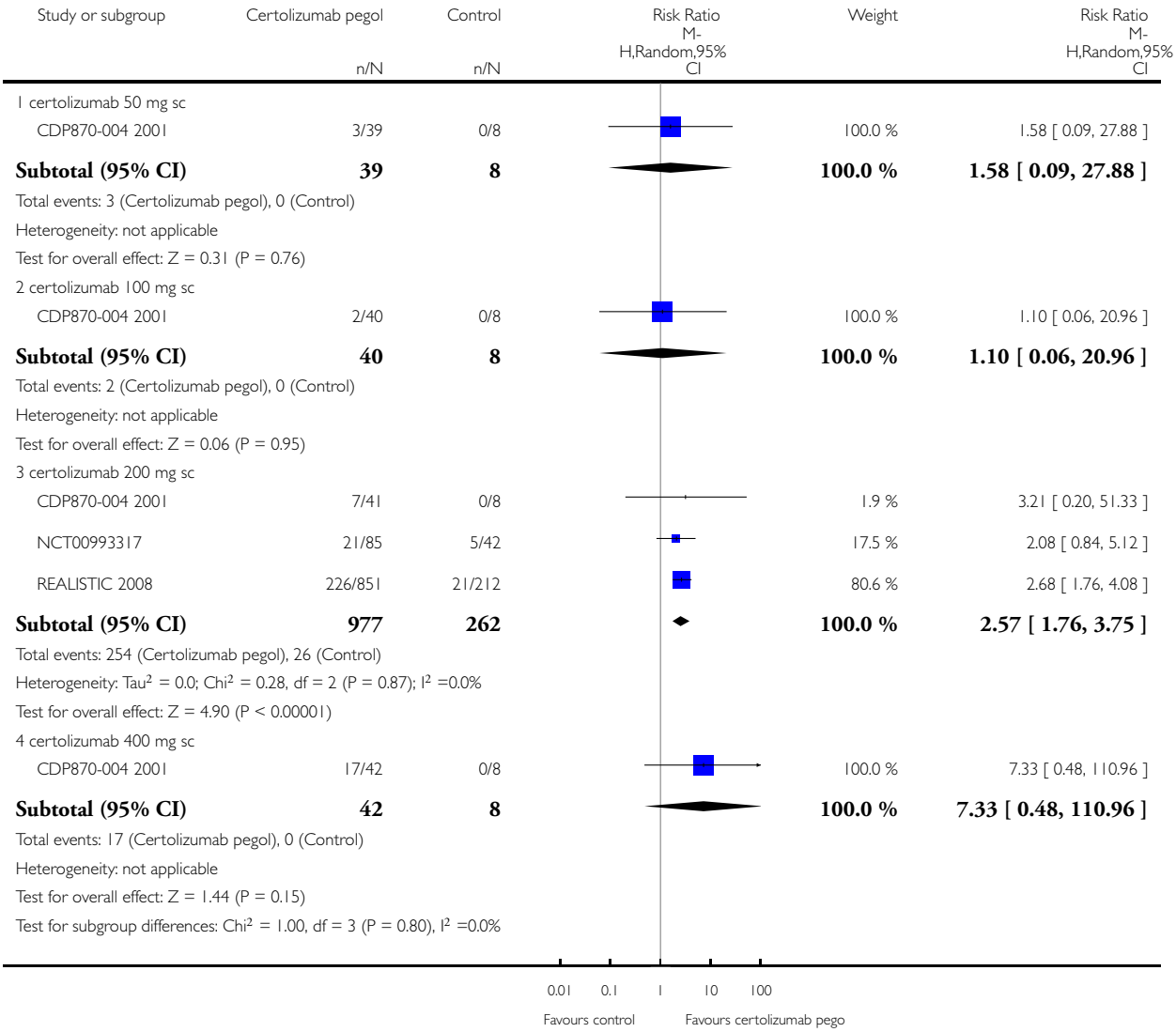
(3) From EMEA report, only data for ACR20

Analysis 1.2. Comparison 1 Efficacy at 12 weeks, any dose, Outcome 2 ACR50.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 1 Efficacy at 12 weeks, any dose

Outcome: 2 ACR50

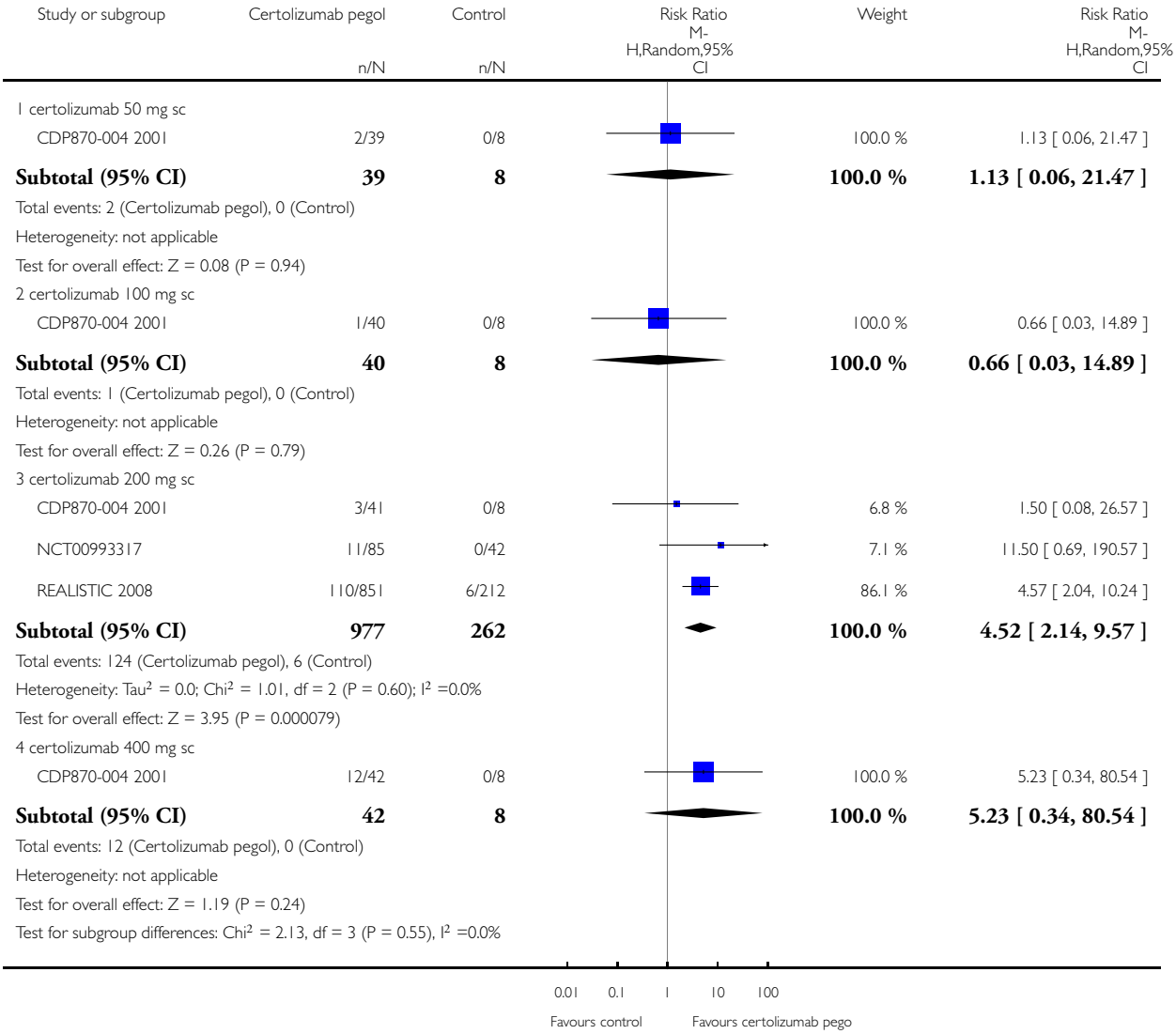


Analysis 1.3. Comparison 1 Efficacy at 12 weeks, any dose, Outcome 3 ACR70.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 1 Efficacy at 12 weeks, any dose

Outcome: 3 ACR70



Analysis 2.1. Comparison 2 Efficacy at 24 weeks, 200 mg certolizumab pegol, Outcome 1 ACR 20.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 2 Efficacy at 24 weeks, 200 mg certolizumab pegol

Outcome: 1 ACR 20

Study or subgroup	Certolizumab pegol 200 mg n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
CERTAIN 2008	35/96	15/98		15.5 %	2.38 [1.39, 4.07]
NCT00993317	54/85	11/42		15.5 %	2.43 [1.42, 4.13]
NCT00791999 JRAPID	60/82	19/77		18.7 %	2.97 [1.96, 4.48]
RAPID1 2005	228/393	27/199		20.1 %	4.28 [2.98, 6.13]
NCT00791921 HIKARI	74/116	13/114		15.6 %	5.59 [3.29, 9.50]
RAPID2 2007	141/246	11/127		14.5 %	6.62 [3.72, 11.76]
Total (95% CI)	**1018**	**657**		**100.0 %**	**3.71 [2.68, 5.13]**

Total events: 592 (Certolizumab pegol 200 mg), 96 (Placebo)

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 13.68$, df = 5 (P = 0.02); $I^2 = 63\%$

Test for overall effect: Z = 7.92 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 Efficacy at 24 weeks, 200 mg certolizumab pegol, Outcome 2 ACR 50.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 2 Efficacy at 24 weeks, 200 mg certolizumab pegol

Outcome: 2 ACR 50

Study or subgroup	Certolizumab pegol 200 mg n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
CERTAIN 2008	20/96	7/98		16.7 %	2.92 [1.29, 6.58]
NCT00791999 JRAPID	45/82	13/77		24.4 %	3.25 [1.91, 5.54]
NCT00993317	35/85	8/42		20.2 %	2.16 [1.10, 4.24]
RAPID1 2005	144/393	15/199		25.3 %	4.86 [2.94, 8.04]
RAPID2 2007	80/246	4/127		13.4 %	10.33 [3.87, 27.54]
Total (95% CI)	**902**	**543**		**100.0 %**	**3.80 [2.42, 5.95]**
Total events: 324 (Certolizumab pegol 200 mg), 47 (Placebo)					
Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 9.05$, df = 4 (P = 0.06); $I^2 = 56\%$					
Test for overall effect: Z = 5.82 (P < 0.00001)					
Test for subgroup differences: Not applicable					

Analysis 2.3. Comparison 2 Efficacy at 24 weeks, 200 mg certolizumab pegol, Outcome 3 ACR 70.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 2 Efficacy at 24 weeks, 200 mg certolizumab pegol

Outcome: 3 ACR 70

Study or subgroup	Certolizumab pegol 200 mg n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
CERTAIN 2008	9/96	3/98		22.4 %	3.06 [0.85, 10.97]
NCT00791999 JRAPID	24/82	1/77		10.0 %	22.54 [3.12, 162.58]
NCT00993317	14/85	1/42		9.8 %	6.92 [0.94, 50.85]
RAPID1 2005	83/393	6/199		47.8 %	7.00 [3.11, 15.76]
RAPID2 2007	39/246	1/127		10.0 %	20.13 [2.80, 144.86]
Total (95% CI)	**902**	**543**		**100.0 %**	**7.26 [3.83, 13.76]**
Total events: 169 (Certolizumab pegol 200 mg), 12 (Placebo)					
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 4.38$, df = 4 (P = 0.36); $I^2 = 9\%$					
Test for overall effect: Z = 6.07 (P < 0.00001)					
Test for subgroup differences: Not applicable					

Analysis 3.1. Comparison 3 Efficacy at 24 weeks, 400 mg certolizumab, Outcome 1 ACR 20.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 3 Efficacy at 24 weeks, 400 mg certolizumab

Outcome: 1 ACR 20

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
CDP870-014 2009	56/126	27/121		21.8 %	1.99 [1.35, 2.93]
FAST4WARD 2005	50/111	10/109		16.9 %	4.91 [2.63, 9.18]
NCT00791999 JRAPID	61/85	19/77		21.2 %	2.91 [1.93, 4.39]
RAPID1 2005	236/390	27/199		22.3 %	4.46 [3.11, 6.39]
RAPID2 2007	141/246	11/127		17.9 %	6.62 [3.72, 11.76]
Total (95% CI)	**958**	**633**		**100.0 %**	**3.73 [2.43, 5.72]**

Total events: 544 (Certolizumab pegol), 94 (Control)

Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 17.77$, df = 4 (P = 0.001); $I^2 = 77\%$

Test for overall effect: Z = 6.03 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 3.2. Comparison 3 Efficacy at 24 weeks, 400 mg certolizumab, Outcome 2 ACR 50.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 3 Efficacy at 24 weeks, 400 mg certolizumab

Outcome: 2 ACR 50

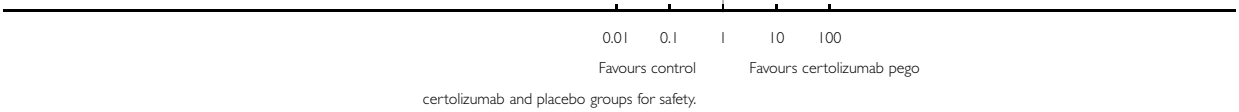
Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
CDP870-014 2009 (1)	22/126	7/121		17.1 %	3.02 [1.34, 6.81]
FAST4WARD 2005	25/111	4/109		12.3 %	6.14 [2.21, 17.05]
NCT00791999 JRAPID	46/85	13/77		27.9 %	3.21 [1.88, 5.46]
RAPID1 2005	155/390	15/199		29.5 %	5.27 [3.19, 8.71]
RAPID2 2007	81/246	4/127		13.1 %	10.45 [3.92, 27.88]
Total (95% CI)	**958**	**633**		**100.0 %**	**4.65 [3.09, 6.99]**

Total events: 329 (Certolizumab pegol), 43 (Control)

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 6.53$, df = 4 (P = 0.16); $I^2 = 39\%$

Test for overall effect: Z = 7.37 (P < 0.00001)

Test for subgroup differences: Not applicable



certolizumab and placebo groups for safety.

(1) EMEA report quotes 126 and 121 patients in certoluzimab and placebo group. Clinical Study Summary (CSS) from UCB quotes n=125 for both groups for effectiveness and 119 and 124 for

Analysis 3.3. Comparison 3 Efficacy at 24 weeks, 400 mg certolizumab, Outcome 3 ACR 70.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 3 Efficacy at 24 weeks, 400 mg certolizumab

Outcome: 3 ACR 70

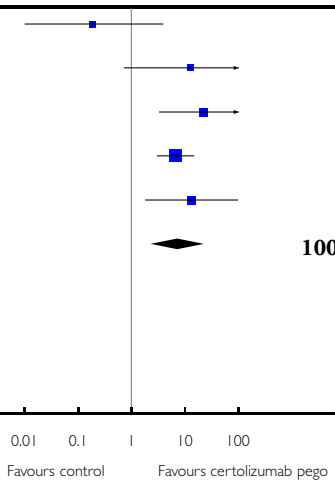
Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
CDP870-014 2009 (1)	0/126	2/121		11.2 %	0.19 [0.01, 3.96]
FAST4WARD 2005	6/111	0/109		12.1 %	12.77 [0.73, 223.93]
NCT00791999 JRAPID	26/85	1/77		19.7 %	23.55 [3.27, 169.46]
RAPID1 2005	80/390	6/199		37.4 %	6.80 [3.02, 15.32]
RAPID2 2007	26/246	1/127		19.6 %	13.42 [1.84, 97.78]
Total (95% CI)	**958**	**633**		**100.0 %**	**7.20 [2.25, 23.03]**

Total events: 138 (Certolizumab pegol), 10 (Control)

Heterogeneity: $Tau^2 = 0.77$; $Chi^2 = 7.46$, df = 4 (P = 0.11); $I^2 = 46\%$

Test for overall effect: Z = 3.33 (P = 0.00088)

Test for subgroup differences: Not applicable



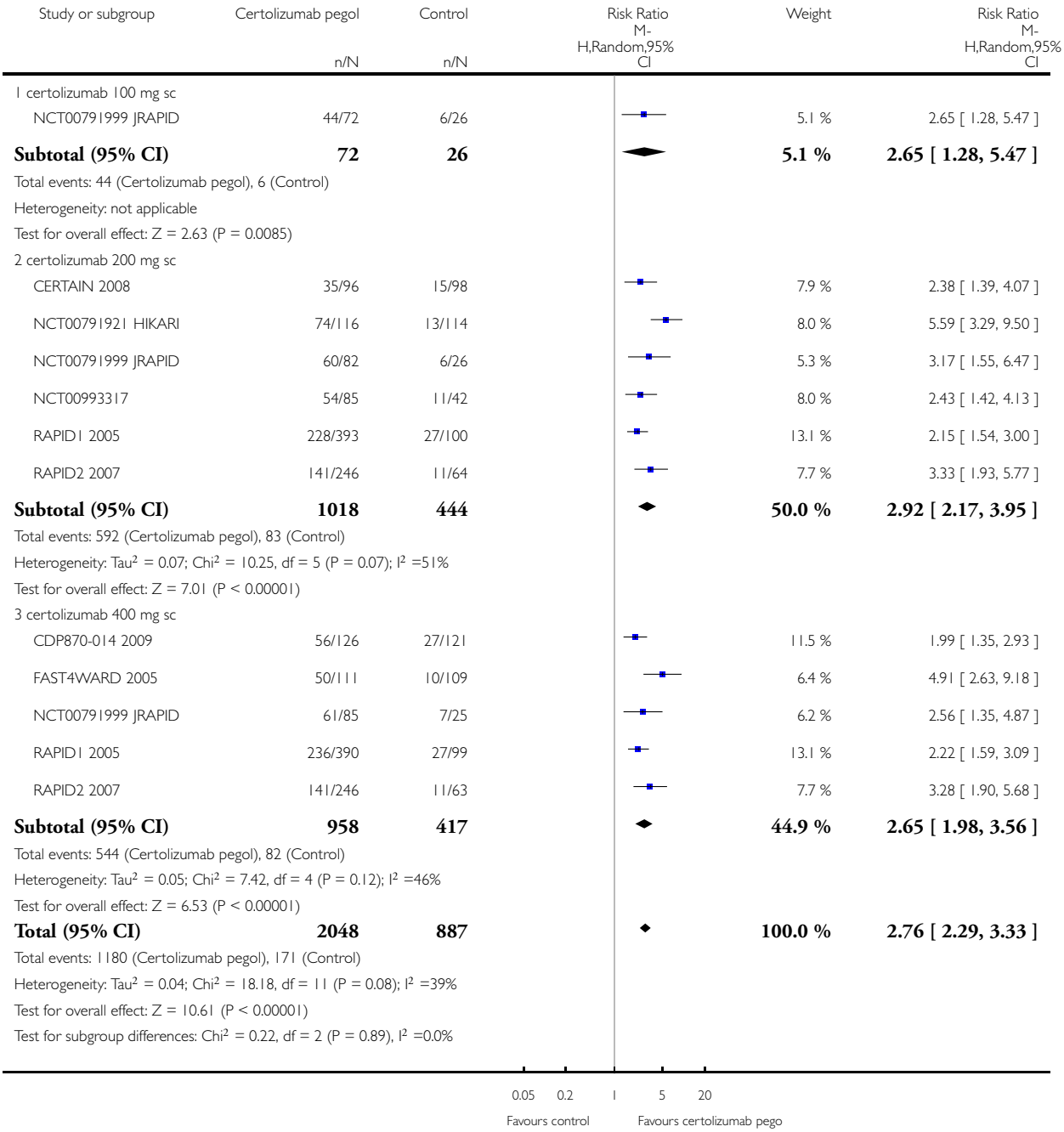
(1) From EMEA report

Analysis 4.1. Comparison 4 Efficacy at 24 weeks, any dose, Outcome 1 ACR20.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 4 Efficacy at 24 weeks, any dose

Outcome: 1 ACR20



Analysis 4.2. Comparison 4 Efficacy at 24 weeks, any dose, Outcome 2 ACR50.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 4 Efficacy at 24 weeks, any dose

Outcome: 2 ACR50

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 certolizumab 100 mg sc					
NCT00791999 JRAPID	32/72	4/26		5.5 %	2.89 [1.13, 7.38]
Subtotal (95% CI)	**72**	**26**		**5.5 %**	**2.89 [1.13, 7.38]**
Total events: 32 (Certolizumab pegol), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.22 (P = 0.027)					
2 certolizumab 200 mg sc					
CERTAIN 2008	20/96	7/98		7.3 %	2.92 [1.29, 6.58]
NCT00791999 JRAPID	45/82	4/26		5.7 %	3.57 [1.42, 8.97]
NCT00993317	35/85	8/42		10.6 %	2.16 [1.10, 4.24]
RAPID1 2005	144/393	15/100		20.5 %	2.44 [1.50, 3.96]
RAPID2 2007	80/246	4/64		5.2 %	5.20 [1.98, 13.67]
Subtotal (95% CI)	**902**	**330**		**49.3 %**	**2.76 [2.02, 3.78]**
Total events: 324 (Certolizumab pegol), 38 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.81, df = 4 (P = 0.59); I^2 =0.0%					
Test for overall effect: Z = 6.37 (P < 0.00001)					
3 certolizumab 400 mg sc					
CDP870-014 2009	22/126	7/121		7.3 %	3.02 [1.34, 6.81]
FAST4WARD 2005	25/111	4/109		4.6 %	6.14 [2.21, 17.05]
NCT00791999 JRAPID	46/85	5/25		7.4 %	2.71 [1.21, 6.07]
RAPID1 2005	155/390	15/99		20.8 %	2.62 [1.62, 4.25]
RAPID2 2007	81/246	4/63		5.2 %	5.19 [1.98, 13.61]
Subtotal (95% CI)	**958**	**417**		**45.2 %**	**3.18 [2.29, 4.41]**
Total events: 329 (Certolizumab pegol), 35 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.42, df = 4 (P = 0.49); I^2 =0.0%					
Test for overall effect: Z = 6.94 (P < 0.00001)					
Total (95% CI)	**1932**	**773**		**100.0 %**	**2.95 [2.37, 3.68]**
Total events: 685 (Certolizumab pegol), 77 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 6.62, df = 10 (P = 0.76); I^2 =0.0%					
Test for overall effect: Z = 9.66 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.38, df = 2 (P = 0.83), I^2 =0.0%					

Analysis 4.3. Comparison 4 Efficacy at 24 weeks, any dose, Outcome 3 ACR70.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 4 Efficacy at 24 weeks, any dose

Outcome: 3 ACR70

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 certolizumab 100 mg sc					
NCT00791999 JRAPID	19/72	1/26		4.9 %	6.86 [0.97, 48.72]
Subtotal (95% CI)	**72**	**26**		**4.9 %**	**6.86 [0.97, 48.72]**
Total events: 19 (Certolizumab pegol), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.93 (P = 0.054)					
2 certolizumab 200 mg sc					
CERTAIN 2008	9/96	3/98		11.7 %	3.06 [0.85, 10.97]
NCT00791999 JRAPID	24/82	0/26		2.5 %	15.94 [1.00, 253.38]
NCT00993317	14/85	1/42		4.8 %	6.92 [0.94, 50.85]
RAPID1 2005	83/393	6/100		29.8 %	3.52 [1.58, 7.83]
RAPID2 2007	39/246	1/64		4.9 %	10.15 [1.42, 72.45]
Subtotal (95% CI)	**902**	**330**		**53.6 %**	**4.29 [2.36, 7.77]**
Total events: 169 (Certolizumab pegol), 11 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.55, df = 4 (P = 0.64); I^2 =0.0%					
Test for overall effect: Z = 4.79 (P < 0.00001)					
3 certolizumab 400 mg sc					
CDP870-014 2009	0/126	2/121		2.1 %	0.19 [0.01, 3.96]
FAST4WARD 2005	6/111	0/109		2.3 %	12.77 [0.73, 223.93]
NCT00791999 JRAPID	26/85	0/25		2.5 %	16.02 [1.01, 253.98]
RAPID1 2005	80/390	6/99		29.7 %	3.38 [1.52, 7.53]
RAPID2 2007	26/246	1/63		4.9 %	6.66 [0.92, 48.13]
Subtotal (95% CI)	**958**	**417**		**41.4 %**	**4.04 [1.37, 11.90]**
Total events: 138 (Certolizumab pegol), 9 (Control)					

(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Heterogeneity: Tau² = 0.50; Chi² = 5.94, df = 4 (P = 0.20); I² =33%					
Test for overall effect: Z = 2.53 (P = 0.011)					
Total (95% CI)	**1932**	**773**	◆	**100.0 %**	**4.15 [2.68, 6.42]**
Total events: 326 (Certolizumab pegol), 21 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 8.81, df = 10 (P = 0.55); I² =0.0%					
Test for overall effect: Z = 6.40 (P < 0.00001)					
Test for subgroup differences: Chi² = 0.23, df = 2 (P = 0.89), I² =0.0%					

Analysis 5.1. Comparison 5 Efficacy at 52 weeks, 200 mg certolizumab, Outcome 1 ACR 20.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 5 Efficacy at 52 weeks, 200 mg certolizumab

Outcome: 1 ACR 20

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RAPID1 2005	208/393	26/199	■	100.0 %	4.05 [2.80, 5.87]
Total (95% CI)	**393**	**199**	◆	**100.0 %**	**4.05 [2.80, 5.87]**
Total events: 208 (Certolizumab pegol), 26 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 7.40 (P < 0.00001)					
Test for subgroup differences: Not applicable					

Analysis 5.2. Comparison 5 Efficacy at 52 weeks, 200 mg certolizumab, Outcome 2 ACR 50.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 5 Efficacy at 52 weeks, 200 mg certolizumab

Outcome: 2 ACR 50

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RAPID1 2005	149/393	15/199		100.0 %	5.03 [3.04, 8.32]
Total (95% CI)	**393**	**199**		**100.0 %**	**5.03 [3.04, 8.32]**
Total events: 149 (Certolizumab pegol), 15 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 6.30 (P < 0.00001)					
Test for subgroup differences: Not applicable					

Analysis 5.3. Comparison 5 Efficacy at 52 weeks, 200 mg certolizumab, Outcome 3 ACR 70.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 5 Efficacy at 52 weeks, 200 mg certolizumab

Outcome: 3 ACR 70

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RAPID1 2005	83/393	7/199		100.0 %	6.00 [2.83, 12.74]
Total (95% CI)	**393**	**199**		**100.0 %**	**6.00 [2.83, 12.74]**
Total events: 83 (Certolizumab pegol), 7 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.67 (P < 0.00001)					
Test for subgroup differences: Not applicable					

Analysis 6.1. Comparison 6 Efficacy at 52 weeks, 400 mg certolizumab, Outcome 1 ACR 20.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 6 Efficacy at 52 weeks, 400 mg certolizumab

Outcome: 1 ACR 20

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RAPID1 2005	213/390	26/199		100.0 %	4.18 [2.89, 6.05]
Total (95% CI)	**390**	**199**		**100.0 %**	**4.18 [2.89, 6.05]**
Total events: 213 (Certolizumab pegol), 26 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 7.58 (P < 0.00001)					
Test for subgroup differences: Not applicable					

Analysis 6.2. Comparison 6 Efficacy at 52 weeks, 400 mg certolizumab, Outcome 2 ACR 50.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 6 Efficacy at 52 weeks, 400 mg certolizumab

Outcome: 2 ACR 50

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RAPID1 2005	155/390	15/199		100.0 %	5.27 [3.19, 8.71]
Total (95% CI)	**390**	**199**		**100.0 %**	**5.27 [3.19, 8.71]**
Total events: 155 (Certolizumab pegol), 15 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 6.49 (P < 0.00001)					
Test for subgroup differences: Not applicable					

Analysis 6.3. Comparison 6 Efficacy at 52 weeks, 400 mg certolizumab, Outcome 3 ACR 70.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 6 Efficacy at 52 weeks, 400 mg certolizumab

Outcome: 3 ACR 70

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RAPID1 2005	90/390	7/199		100.0 %	6.56 [3.10, 13.89]
Total (95% CI)	**390**	**199**		**100.0 %**	**6.56 [3.10, 13.89]**
Total events: 90 (Certolizumab pegol), 7 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.92 (P < 0.00001)					
Test for subgroup differences: Not applicable					

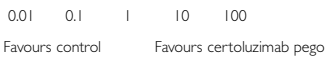
Analysis 7.1. Comparison 7 Efficacy at 52 weeks, any dose, Outcome 1 ACR20.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 7 Efficacy at 52 weeks, any dose

Outcome: 1 ACR20

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 certolizumab 200 mg sc					
RAPID1 2005	208/393	26/100		49.8 %	2.04 [1.44, 2.87]
Subtotal (95% CI)	**393**	**100**		**49.8 %**	**2.04 [1.44, 2.87]**
Total events: 208 (Certolizumab pegol), 26 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.06 (P = 0.000050)					
2 certolizumab 400 mg sc					
RAPID1 2005	213/390	26/99		50.2 %	2.08 [1.48, 2.93]
Subtotal (95% CI)	**390**	**99**		**50.2 %**	**2.08 [1.48, 2.93]**
Total events: 213 (Certolizumab pegol), 26 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.19 (P = 0.000028)					
Total (95% CI)	**783**	**199**		**100.0 %**	**2.06 [1.61, 2.62]**
Total events: 421 (Certolizumab pegol), 52 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.01, df = 1 (P = 0.93); I^2 =0.0%					
Test for overall effect: Z = 5.83 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.01, df = 1 (P = 0.93), I^2 =0.0%					



Analysis 7.2. Comparison 7 Efficacy at 52 weeks, any dose, Outcome 2 ACR50.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 7 Efficacy at 52 weeks, any dose

Outcome: 2 ACR50

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 certolizumab 200 mg sc					
RAPID1 2005	149/393	15/100		49.8 %	2.53 [1.56, 4.10]
Subtotal (95% CI)	**393**	**100**		**49.8 %**	**2.53 [1.56, 4.10]**
Total events: 149 (Certolizumab pegol), 15 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.76 (P = 0.00017)					
2 certolizumab 400 mg sc					
RAPID1 2005	155/390	15/99		50.2 %	2.62 [1.62, 4.25]
Subtotal (95% CI)	**390**	**99**		**50.2 %**	**2.62 [1.62, 4.25]**
Total events: 155 (Certolizumab pegol), 15 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.92 (P = 0.000088)					
Total (95% CI)	**783**	**199**		**100.0 %**	**2.58 [1.83, 3.62]**
Total events: 304 (Certolizumab pegol), 30 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.01, df = 1 (P = 0.92); I^2 =0.0%					
Test for overall effect: Z = 5.43 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.01, df = 1 (P = 0.92), I^2 =0.0%					

Analysis 7.3. Comparison 7 Efficacy at 52 weeks, any dose, Outcome 3 ACR70.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 7 Efficacy at 52 weeks, any dose

Outcome: 3 ACR70

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 certolizumab 200 mg sc					
RAPID1 2005	83/393	7/100		49.8 %	3.02 [1.44, 6.32]
Subtotal (95% CI)	**393**	**100**		**49.8 %**	**3.02 [1.44, 6.32]**
Total events: 83 (Certolizumab pegol), 7 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.93 (P = 0.0034)					
2 certolizumab 400 mg sc					
RAPID1 2005	90/390	7/99		50.2 %	3.26 [1.56, 6.82]
Subtotal (95% CI)	**390**	**99**		**50.2 %**	**3.26 [1.56, 6.82]**
Total events: 90 (Certolizumab pegol), 7 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.15 (P = 0.0017)					
Total (95% CI)	**783**	**199**		**100.0 %**	**3.14 [1.86, 5.29]**
Total events: 173 (Certolizumab pegol), 14 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.02, df = 1 (P = 0.88); I^2 =0.0%					
Test for overall effect: Z = 4.29 (P = 0.000017)					
Test for subgroup differences: Chi^2 = 0.02, df = 1 (P = 0.88), I^2 =0.0%					

Analysis 8.1. Comparison 8 Safety, certolizumab 200 mg, Outcome 1 Any adverse event.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 1 Any adverse event

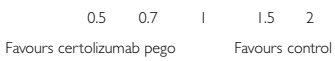
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
CERTAIN 2008	37/96	41/98		7.4 %	0.92 [0.65, 1.30]
NCT00791921 HIKARI (1)	59/116	44/114		9.5 %	1.32 [0.98, 1.77]
NCT00791999 JRAPID	48/82	31/77		8.0 %	1.45 [1.05, 2.02]
NCT00993317	60/85	21/42		7.8 %	1.41 [1.01, 1.97]
RAPID1 2005	293/392	115/199		24.4 %	1.29 [1.13, 1.48]
RAPID2 2007	139/248	66/125		16.2 %	1.06 [0.87, 1.30]
REALISTIC 2008	571/846	129/209		26.7 %	1.09 [0.97, 1.23]
Total (95% CI)	**1865**	**864**		**100.0 %**	**1.19 [1.07, 1.32]**

Total events: 1207 (Certolizumab pegol 200 mg), 447 (Control)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 9.80$, df = 6 (P = 0.13); $I^2 = 39\%$

Test for overall effect: Z = 3.29 (P = 0.00099)

Test for subgroup differences: Not applicable



(1) UCB provides us different number of AE that appears in clinicaltrials.org. 67 in CZP 200 mg and 83 in control groups Check with UCB again

Analysis 8.2. Comparison 8 Safety, certolizumab 200 mg, Outcome 2 Adverse events Intensity mild.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 2 Adverse events Intensity mild

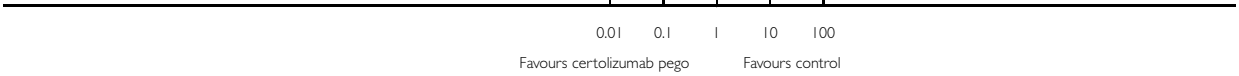
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
NCT00791921 HIKARI (1)	29/116	33/114		12.7 %	0.86 [0.56, 1.32]
RAPID1 2005	244/392	90/199		37.2 %	1.38 [1.16, 1.63]
RAPID2 2007	108/248	45/125		23.6 %	1.21 [0.92, 1.59]
REALISTIC 2008	248/846	56/209		26.5 %	1.09 [0.85, 1.40]
Total (95% CI)	**1602**	**647**		**100.0 %**	**1.18 [1.00, 1.41]**

Total events: 629 (Certolizumab pegol 200 mg), 224 (Control)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 5.26$, df = 3 (P = 0.15); $I^2 = 43\%$

Test for overall effect: Z = 1.94 (P = 0.053)

Test for subgroup differences: Not applicable



(1) UCB provides us different number of AE that appears in clinicaltrials.org

Analysis 8.3. Comparison 8 Safety, certolizumab 200 mg, Outcome 3 Adverse events Intensity moderate.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 3 Adverse events Intensity moderate

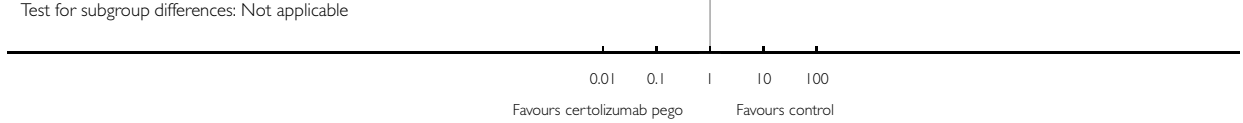
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
NCT00791921 HIKARI	36/116	44/114		20.2 %	0.80 [0.56, 1.15]
RAPID1 2005	174/392	66/199		30.9 %	1.34 [1.07, 1.68]
RAPID2 2007	61/248	32/125		19.4 %	0.96 [0.66, 1.39]
REALISTIC 2008	257/846	58/209		29.5 %	1.09 [0.86, 1.39]
Total (95% CI)	**1602**	**647**		**100.0 %**	**1.07 [0.86, 1.32]**

Total events: 528 (Certolizumab pegol 200 mg), 200 (Control)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 6.36$, df = 3 (P = 0.10); $I^2 = 53\%$

Test for overall effect: Z = 0.61 (P = 0.54)

Test for subgroup differences: Not applicable



Analysis 8.4. Comparison 8 Safety, certolizumab 200 mg, Outcome 4 Adverse events Intensity severe.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 4 Adverse events Intensity severe

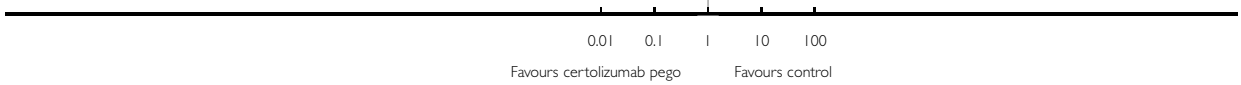
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
NCT00791921 HIKARI	2/116	6/114		7.0 %	0.35 [0.09, 1.43]
REALISTIC 2008	66/846	15/209		42.8 %	1.09 [0.62, 1.93]
RAPID1 2005	32/392	13/199		33.5 %	1.26 [0.66, 2.40]
RAPID2 2007	17/248	5/125		16.7 %	1.67 [0.67, 4.16]
Total (95% CI)	**1602**	**647**		**100.0 %**	**1.14 [0.78, 1.65]**

Total events: 117 (Certolizumab pegol 200 mg), 39 (Control)

Heterogeneity: $Chi^2 = 3.49$, df = 3 (P = 0.32); $I^2 = 14\%$

Test for overall effect: Z = 0.67 (P = 0.50)

Test for subgroup differences: Not applicable



Analysis 8.5. Comparison 8 Safety, certolizumab 200 mg, Outcome 5 Adverse events related to study drug.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 5 Adverse events related to study drug

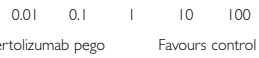
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
RAPID1 2005	167/392	50/199		72.2 %	1.70 [1.30, 2.21]
RAPID2 2007	61/248	23/125		27.8 %	1.34 [0.87, 2.05]
Total (95% CI)	**640**	**324**		**100.0 %**	**1.59 [1.27, 1.99]**

Total events: 228 (Certolizumab pegol 200 mg), 73 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.85$, df = 1 (P = 0.36); $I^2 = 0.0\%$

Test for overall effect: Z = 4.01 (P = 0.000062)

Test for subgroup differences: Not applicable



Analysis 8.6. Comparison 8 Safety, certolizumab 200 mg, Outcome 6 Serious Adverse Events (SAE).

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 6 Serious Adverse Events (SAE)

Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CERTAIN 2008	5/96	7/98		8.1 %	0.72 [0.22, 2.30]
REALISTIC 2008	52/846	12/209		27.3 %	1.07 [0.57, 2.02]
RAPID1 2005	45/392	11/199		32.4 %	2.00 [1.12, 3.58]
RAPID2 2007	18/248	4/125		13.2 %	2.07 [0.83, 5.16]
NCT00791999 JRAPID	4/82	1/77		3.5 %	3.21 [0.54, 19.00]
NCT00791921 HIKARI	13/116	3/114		10.7 %	3.74 [1.36, 10.31]
NCT00993317	8/85	0/42		4.8 %	4.86 [1.07, 22.14]
Total (95% CI)	**1865**	**864**		**100.0 %**	**1.77 [1.27, 2.46]**

Total events: 145 (Certolizumab pegol 200 mg), 38 (Control)

Heterogeneity: $Chi^2 = 9.21$, df = 6 (P = 0.16); $I^2 = 35\%$

Test for overall effect: Z = 3.38 (P = 0.00074)

Test for subgroup differences: Not applicable

Analysis 8.7. Comparison 8 Safety, certolizumab 200 mg, Outcome 7 Serious Infections.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 7 Serious Infections

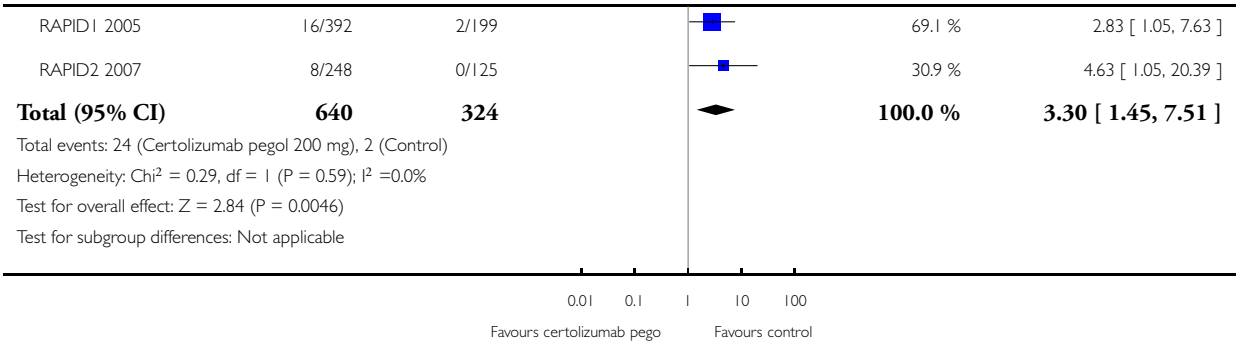
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID1 2005	16/392	2/199		69.1 %	2.83 [1.05, 7.63]
RAPID2 2007	8/248	0/125		30.9 %	4.63 [1.05, 20.39]
Total (95% CI)	**640**	**324**		**100.0 %**	**3.30 [1.45, 7.51]**

Total events: 24 (Certolizumab pegol 200 mg), 2 (Control)

Heterogeneity: $Chi^2 = 0.29$, df = 1 (P = 0.59); $I^2 = 0.0\%$

Test for overall effect: Z = 2.84 (P = 0.0046)

Test for subgroup differences: Not applicable



Analysis 8.8. Comparison 8 Safety, certolizumab 200 mg, Outcome 8 Adverse events leading to death.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 8 Adverse events leading to death

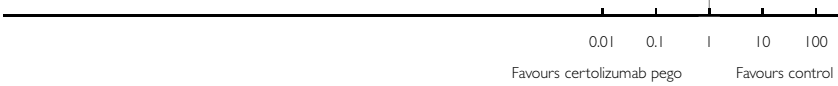
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CERTAIN 2008	0/96	0/98			Not estimable
NCT00791921 HIKARI (1)	1/116	0/114		17.1 %	7.26 [0.14, 366.07]
RAPID1 2005	2/392	1/199		45.8 %	1.02 [0.09, 11.18]
RAPID2 2007	1/248	0/125		15.3 %	4.50 [0.07, 286.06]
REALISTIC 2008	2/846	0/209		21.8 %	3.48 [0.11, 112.96]
Total (95% CI)	**1698**	**745**		**100.0 %**	**2.34 [0.46, 11.84]**

Total events: 6 (Certolizumab pegol 200 mg), 1 (Control)

Heterogeneity: $Chi^2 = 0.93$, df = 3 (P = 0.82); $I^2 = 0.0\%$

Test for overall effect: Z = 1.02 (P = 0.31)

Test for subgroup differences: Not applicable



(1) 1 patient died of a rupture of a dissecting aortic aneurysm in the thoracic region, but UCB considered that in unlikely to have beeen related to study medication

Analysis 8.9. Comparison 8 Safety, certolizumab 200 mg, Outcome 9 Adverse events leading to withdrawal.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 9 Adverse events leading to withdrawal

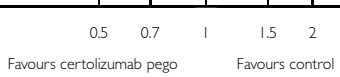
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CERTAIN 2008	6/96	6/98		12.5 %	1.02 [0.32, 3.28]
NCT00791921 HIKARI	8/116	2/114		10.6 %	3.42 [0.97, 12.13]
NCT00791999 JRAPID	3/82	3/77		6.4 %	0.94 [0.18, 4.77]
NCT00993317	4/85	2/42		5.6 %	0.99 [0.17, 5.60]
RAPID1 2005	17/392	3/199		19.1 %	2.37 [0.92, 6.09]
RAPID2 2007	12/248	2/125		13.3 %	2.45 [0.79, 7.57]
REALISTIC 2008	40/846	8/209		32.3 %	1.23 [0.60, 2.54]
Total (95% CI)	**1865**	**864**		**100.0 %**	**1.62 [1.07, 2.44]**

Total events: 90 (Certolizumab pegol 200 mg), 26 (Control)

Heterogeneity: $Chi^2 = 4.38$, df = 6 (P = 0.62); $I^2 = 0.0\%$

Test for overall effect: Z = 2.28 (P = 0.022)

Test for subgroup differences: Not applicable



Favours certolizumab pego Favours control

Analysis 8.10. Comparison 8 Safety, certolizumab 200 mg, Outcome 10 Death.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 10 Death

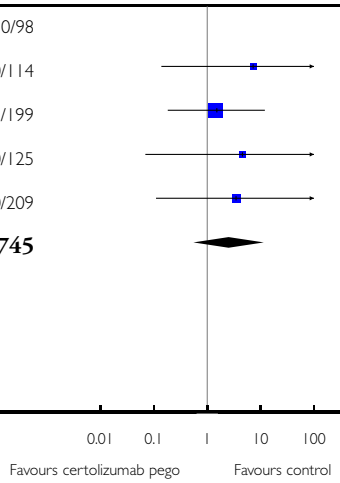
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CERTAIN 2008	0/96	0/98			Not estimable
NCT00791921 HIKARI (1)	1/116	0/114		14.9 %	7.26 [0.14, 366.07]
RAPID1 2005 (2)	3/392	1/199		52.9 %	1.48 [0.18, 11.81]
RAPID2 2007	1/246	0/125		13.3 %	4.52 [0.07, 285.66]
REALISTIC 2008	2/846	0/209		18.9 %	3.48 [0.11, 112.96]
Total (95% CI)	**1696**	**745**		**100.0 %**	**2.56 [0.56, 11.59]**

Total events: 7 (Certolizumab pegol 200 mg), 1 (Control)

Heterogeneity: $Chi^2 = 0.64$, df = 3 (P = 0.89); $I^2 = 0.0\%$

Test for overall effect: Z = 1.22 (P = 0.22)

Test for subgroup differences: Not applicable



(1) 1 patient died of a rupture of a dissecting aortic aneurysm in the thoracic region, but UCB considered that in unlikely to have beeen related to study medication

(2) One patient died of hepatic neoplam and other for cardiac arrest. One patient died in placebo group of a myocardial infarction

Analysis 8.11. Comparison 8 Safety, certolizumab 200 mg, Outcome 11 Tuberculosis.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 11 Tuberculosis

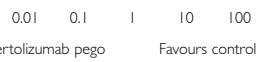
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CERTAIN 2008	0/96	0/98			Not estimable
NCT00993317	2/85	0/42		28.3 %	4.51 [0.23, 86.80]
RAPID1 2005	2/392	0/199		28.8 %	4.53 [0.24, 85.22]
RAPID2 2007	3/248	0/125		42.9 %	4.54 [0.41, 50.19]
REALISTIC 2008	0/846	0/209			Not estimable
Total (95% CI)	**1667**	**673**		**100.0 %**	**4.53 [0.94, 21.85]**

Total events: 7 (Certolizumab pegol 200 mg), 0 (Control)

Heterogeneity: $Chi^2 = 0.00$, df = 2 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 1.88 (P = 0.060)

Test for subgroup differences: Not applicable



Analysis 8.12. Comparison 8 Safety, certolizumab 200 mg, Outcome 12 Malignancies included lymphoma.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 12 Malignancies included lymphoma

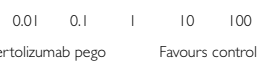
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CERTAIN 2008	0/96	2/98		12.7 %	0.14 [0.01, 2.20]
NCT00791921 HIKARI	0/116	1/114		6.4 %	0.13 [0.00, 6.70]
NCT00993317 (1)	0/85	0/42			Not estimable
RAPID1 2005 (2)	7/392	1/199		45.2 %	2.61 [0.60, 11.41]
RAPID2 2007	1/248	1/125		11.4 %	0.48 [0.03, 9.01]
REALISTIC 2008	4/846	2/209		24.3 %	0.43 [0.06, 3.18]
Total (95% CI)	**1783**	**787**		**100.0 %**	**0.79 [0.29, 2.12]**

Total events: 12 (Certolizumab pegol 200 mg), 7 (Control)

Heterogeneity: Chi^2 = 5.32, df = 4 (P = 0.26); I^2 =25%

Test for overall effect: Z = 0.48 (P = 0.63)

Test for subgroup differences: Not applicable



system], one adrenal adenoma, one hepatic neoplasm one esophageal carcinoma, and uterine cancer

(1) Data provided by UCB

(2) One patient in the arm of placebo suffered a thyroid neoplasm and 7 in the arm of certolizumab 200 mg sc suffered: three basal cell carcinomas [one with metastasis to the central nervous

Analysis 8.13. Comparison 8 Safety, certolizumab 200 mg, Outcome 13 Injection site pain.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 13 Injection site pain

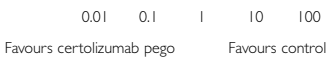
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
NCT00993317	0/85	2/42		19.9 %	0.05 [0.00, 0.91]
RAPID1 2005	8/392	0/199		80.1 %	4.60 [1.05, 20.10]
RAPID2 2007	0/248	0/125			Not estimable
Total (95% CI)	**725**	**366**		**100.0 %**	**1.85 [0.49, 6.92]**

Total events: 8 (Certolizumab pegol 200 mg), 2 (Control)

Heterogeneity: $Chi^2 = 7.36$, $df = 1$ ($P = 0.01$); $I^2 = 86\%$

Test for overall effect: $Z = 0.91$ ($P = 0.36$)

Test for subgroup differences: Not applicable



Analysis 8.14. Comparison 8 Safety, certolizumab 200 mg, Outcome 14 Injection side reactions.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 14 Injection side reactions

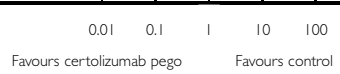
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
NCT00791999 JRAPID	1/82	0/77		2.4 %	6.95 [0.14, 351.04]
RAPID1 2005	9/392	0/199		18.7 %	4.61 [1.15, 18.55]
RAPID2 2007	3/248	0/125		6.3 %	4.54 [0.41, 50.19]
REALISTIC 2008	49/846	2/209		72.7 %	2.86 [1.41, 5.79]
Total (95% CI)	**1568**	**610**		**100.0 %**	**3.28 [1.80, 5.99]**

Total events: 62 (Certolizumab pegol 200 mg), 2 (Control)

Heterogeneity: $Chi^2 = 0.59$, df = 3 (P = 0.90); $I^2 = 0.0\%$

Test for overall effect: Z = 3.87 (P = 0.00011)

Test for subgroup differences: Not applicable



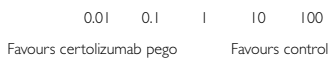
Analysis 8.15. Comparison 8 Safety, certolizumab 200 mg, Outcome 15 Neutralising Anti-certolizumab pegol antibodies.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 15 Neutralising Anti-certolizumab pegol antibodies

Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID2 2007	5/248	0/125		100.0 %	4.57 [0.71, 29.59]
Total (95% CI)	**248**	**125**		**100.0 %**	**4.57 [0.71, 29.59]**
Total events: 5 (Certolizumab pegol 200 mg), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.60 (P = 0.11)					
Test for subgroup differences: Not applicable					



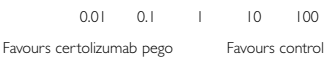
Analysis 8.16. Comparison 8 Safety, certolizumab 200 mg, Outcome 16 Systemic lupus erythematosus.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 16 Systemic lupus erythematosus

Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CERTAIN 2008	0/96	0/98			Not estimable
RAPID2 2007	1/248	0/125		100.0 %	4.50 [0.07, 286.06]
Total (95% CI)	**344**	**223**		**100.0 %**	**4.50 [0.07, 286.06]**
Total events: 1 (Certolizumab pegol 200 mg), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.71 (P = 0.48)					
Test for subgroup differences: Not applicable					



Analysis 8.17. Comparison 8 Safety, certolizumab 200 mg, Outcome 17 Prolonged activated partial thromboplastin time (aPTT).

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 17 Prolonged activated partial thromboplastin time (aPTT)

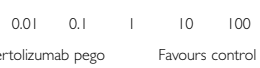
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
NCT00993317	3/85	0/42		17.8 %	4.56 [0.40, 51.56]
RAPID2 2007	12/248	2/125		82.2 %	2.45 [0.79, 7.57]
Total (95% CI)	**333**	**167**		**100.0 %**	**2.73 [0.98, 7.61]**

Total events: 15 (Certolizumab pegol 200 mg), 2 (Control)

Heterogeneity: $Chi^2 = 0.21$, df = 1 (P = 0.65); $I^2 = 0.0\%$

Test for overall effect: Z = 1.92 (P = 0.054)

Test for subgroup differences: Not applicable



Analysis 8.18. Comparison 8 Safety, certolizumab 200 mg, Outcome 18 Urinary tract infection.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 18 Urinary tract infection

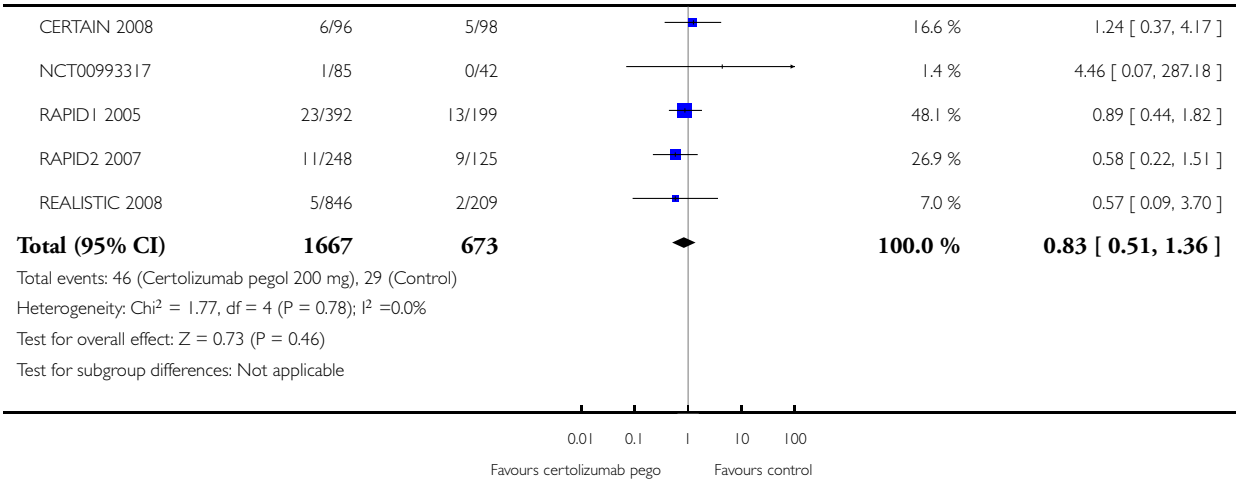
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CERTAIN 2008	6/96	5/98		16.6 %	1.24 [0.37, 4.17]
NCT00993317	1/85	0/42		1.4 %	4.46 [0.07, 287.18]
RAPID1 2005	23/392	13/199		48.1 %	0.89 [0.44, 1.82]
RAPID2 2007	11/248	9/125		26.9 %	0.58 [0.22, 1.51]
REALISTIC 2008	5/846	2/209		7.0 %	0.57 [0.09, 3.70]
Total (95% CI)	**1667**	**673**		**100.0 %**	**0.83 [0.51, 1.36]**

Total events: 46 (Certolizumab pegol 200 mg), 29 (Control)

Heterogeneity: $Chi^2 = 1.77$, df = 4 (P = 0.78); $I^2 = 0.0\%$

Test for overall effect: Z = 0.73 (P = 0.46)

Test for subgroup differences: Not applicable



Analysis 8.19. Comparison 8 Safety, certolizumab 200 mg, Outcome 19 Upper respiratory tract infection.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 19 Upper respiratory tract infection

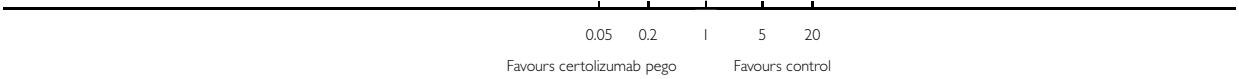
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CERTAIN 2008	6/96	4/98		6.7 %	1.55 [0.44, 5.53]
NCT00791921 HIKARI	3/116	4/114		4.8 %	0.73 [0.16, 3.29]
NCT00791999 JRAPID	2/82	3/77		3.4 %	0.62 [0.11, 3.67]
NCT00993317	12/85	5/42		9.2 %	1.21 [0.41, 3.56]
RAPID1 2005	24/392	5/199		17.2 %	2.16 [0.98, 4.77]
RAPID2 2007	11/248	2/125		7.8 %	2.32 [0.72, 7.47]
REALISTIC 2008	112/846	19/209		51.0 %	1.46 [0.93, 2.32]
Total (95% CI)	**1865**	**864**		**100.0 %**	**1.51 [1.08, 2.09]**

Total events: 170 (Certolizumab pegol 200 mg), 42 (Control)

Heterogeneity: $Chi^2 = 3.35$, df = 6 (P = 0.76); $I^2 = 0.0\%$

Test for overall effect: Z = 2.45 (P = 0.014)

Test for subgroup differences: Not applicable



Analysis 8.20. Comparison 8 Safety, certolizumab 200 mg, Outcome 20 Lower respiratory tract infection/ lung infection.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 20 Lower respiratory tract infection/ lung infection

Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CERTAIN 2008	0/96	1/98		6.9 %	0.14 [0.00, 6.96]
NCT00791921 HIKARI (1)	2/116	0/114		13.8 %	7.33 [0.46, 117.85]
NCT00791999 JRAPID	1/82	1/77		13.7 %	0.94 [0.06, 15.16]
NCT00993317	2/85	0/42		12.2 %	4.51 [0.23, 86.80]
RAPID1 2005	3/392	0/199		18.5 %	4.54 [0.41, 49.96]
REALISTIC 2008	7/846	1/209		34.9 %	1.59 [0.28, 9.09]
Total (95% CI)	**1617**	**739**		**100.0 %**	**2.12 [0.76, 5.95]**

Total events: 15 (Certolizumab pegol 200 mg), 3 (Control)

Heterogeneity: $Chi^2 = 3.70$, df = 5 (P = 0.59); $I^2 = 0.0\%$

Test for overall effect: Z = 1.43 (P = 0.15)

Test for subgroup differences: Not applicable

(1) 2(1 pneumonia neumococcal and 1 pneumocystis jirobenzi pneumonia)

Analysis 8.21. Comparison 8 Safety, certolizumab 200 mg, Outcome 21 Headache.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 21 Headache

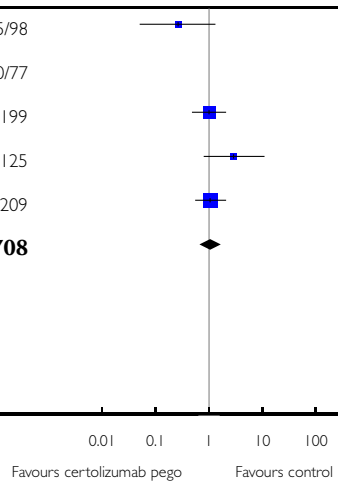
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CERTAIN 2008	1/96	5/98		7.6 %	0.26 [0.05, 1.31]
NCT00791999 JRAPID	0/82	0/77			Not estimable
RAPID1 2005	22/392	11/199		36.1 %	1.02 [0.48, 2.13]
RAPID2 2007	9/248	1/125		11.3 %	2.95 [0.78, 11.14]
REALISTIC 2008	47/846	11/209		45.1 %	1.06 [0.54, 2.05]
Total (95% CI)	**1664**	**708**		**100.0 %**	**1.05 [0.67, 1.64]**

Total events: 79 (Certolizumab pegol 200 mg), 28 (Control)

Heterogeneity: $Chi^2 = 5.18$, df = 3 (P = 0.16); $I^2 = 42\%$

Test for overall effect: Z = 0.22 (P = 0.82)

Test for subgroup differences: Not applicable



Analysis 8.22. Comparison 8 Safety, certolizumab 200 mg, Outcome 22 Bacteriuria.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 22 Bacteriuria

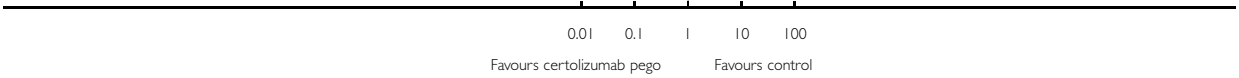
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID2 2007	8/248	4/125		100.0 %	1.01 [0.30, 3.40]
Total (95% CI)	**248**	**125**		**100.0 %**	**1.01 [0.30, 3.40]**

Total events: 8 (Certolizumab pegol 200 mg), 4 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.01 (P = 0.99)

Test for subgroup differences: Not applicable



Analysis 8.23. Comparison 8 Safety, certolizumab 200 mg, Outcome 23 Nasopharyngitis/Pharyngitis.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 23 Nasopharyngitis/Pharyngitis

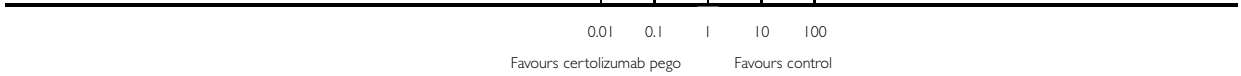
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CERTAIN 2008	10/96	11/98		15.8 %	0.92 [0.37, 2.27]
NCT00791921 HIKARI	26/116	21/114		31.5 %	1.28 [0.67, 2.42]
NCT00791999 JRAPID	16/82	12/77		19.5 %	1.31 [0.58, 2.95]
NCT00993317	10/85	4/42		9.3 %	1.25 [0.39, 4.06]
RAPID1 2005	21/392	3/199		17.3 %	2.68 [1.13, 6.36]
RAPID2 2007	8/248	1/125		6.6 %	2.79 [0.69, 11.32]
Total (95% CI)	**1019**	**655**		**100.0 %**	**1.46 [1.02, 2.09]**

Total events: 91 (Certolizumab pegol 200 mg), 52 (Control)

Heterogeneity: $Chi^2 = 4.04$, df = 5 (P = 0.54); $I^2 = 0.0\%$

Test for overall effect: Z = 2.05 (P = 0.040)

Test for subgroup differences: Not applicable



Analysis 8.24. Comparison 8 Safety, certolizumab 200 mg, Outcome 24 Hypertension.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 24 Hypertension

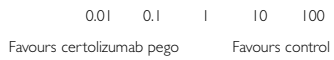
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
NCT00791921 HIKARI	4/116	1/114		13.0 %	3.33 [0.57, 19.54]
NCT00791999 JRAPID	3/82	0/77		7.8 %	7.13 [0.73, 69.59]
RAPID1 2005	25/392	2/199		60.8 %	3.42 [1.51, 7.74]
RAPID2 2007	6/248	2/125		18.4 %	1.48 [0.34, 6.50]
Total (95% CI)	**838**	**515**		**100.0 %**	**3.09 [1.64, 5.84]**

Total events: 38 (Certolizumab pegol 200 mg), 5 (Control)

Heterogeneity: Chi^2 = 1.54, df = 3 (P = 0.67); I^2 =0.0%

Test for overall effect: Z = 3.48 (P = 0.00051)

Test for subgroup differences: Not applicable



Analysis 8.25. Comparison 8 Safety, certolizumab 200 mg, Outcome 25 Hematuria.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 25 Hematuria

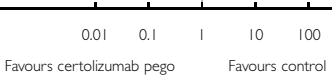
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID2 2007	4/248	5/125		100.0 %	0.36 [0.09, 1.47]
Total (95% CI)	**248**	**125**		**100.0 %**	**0.36 [0.09, 1.47]**

Total events: 4 (Certolizumab pegol 200 mg), 5 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.42 (P = 0.16)

Test for subgroup differences: Not applicable



Analysis 8.26. Comparison 8 Safety, certolizumab 200 mg, Outcome 26 Hepatic enzyme increased.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 26 Hepatic enzyme increased

Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
NCT00791999 JRAPID	3/82	4/77		52.3 %	0.70 [0.15, 3.15]
RAPID2 2007	3/248	4/125		47.7 %	0.34 [0.07, 1.66]
Total (95% CI)	**330**	**202**		**100.0 %**	**0.49 [0.17, 1.48]**
Total events: 6 (Certolizumab pegol 200 mg), 8 (Control)					
Heterogeneity: Chi^2 = 0.41, df = 1 (P = 0.52); I^2 =0.0%					
Test for overall effect: Z = 1.26 (P = 0.21)					
Test for subgroup differences: Not applicable					

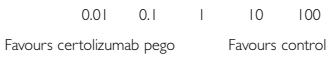
Analysis 8.27. Comparison 8 Safety, certolizumab 200 mg, Outcome 27 AST increased.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 27 AST increased

Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID2 2007	2/248	5/125		100.0 %	0.18 [0.04, 0.86]
Total (95% CI)	**248**	**125**		**100.0 %**	**0.18 [0.04, 0.86]**
Total events: 2 (Certolizumab pegol 200 mg), 5 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.14 (P = 0.032)					
Test for subgroup differences: Not applicable					



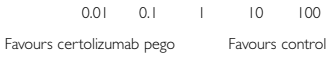
Analysis 8.28. Comparison 8 Safety, certolizumab 200 mg, Outcome 28 ALT increased.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 28 ALT increased

Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID2 2007	1/248	6/125		100.0 %	0.09 [0.02, 0.45]
Total (95% CI)	**248**	**125**		**100.0 %**	**0.09 [0.02, 0.45]**
Total events: 1 (Certolizumab pegol 200 mg), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.95 (P = 0.0032)					
Test for subgroup differences: Not applicable					

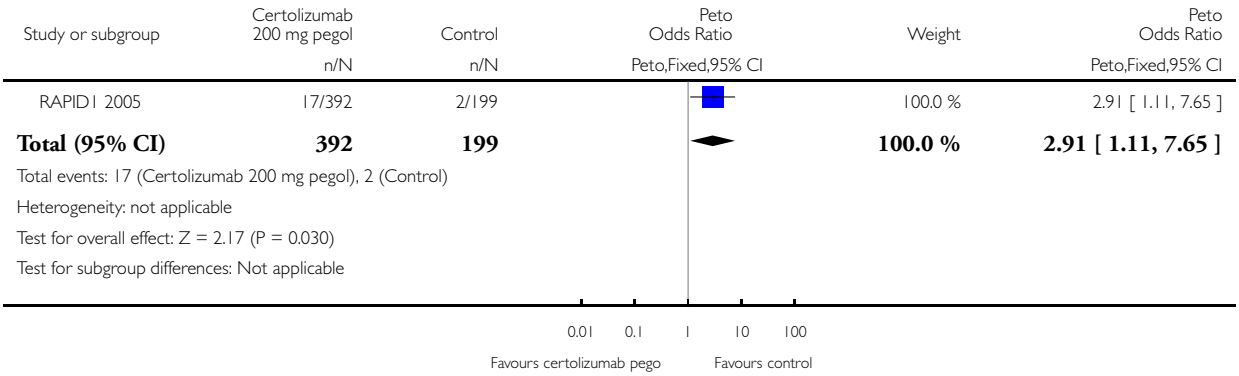


Analysis 8.29. Comparison 8 Safety, certolizumab 200 mg, Outcome 29 Back pain.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 29 Back pain

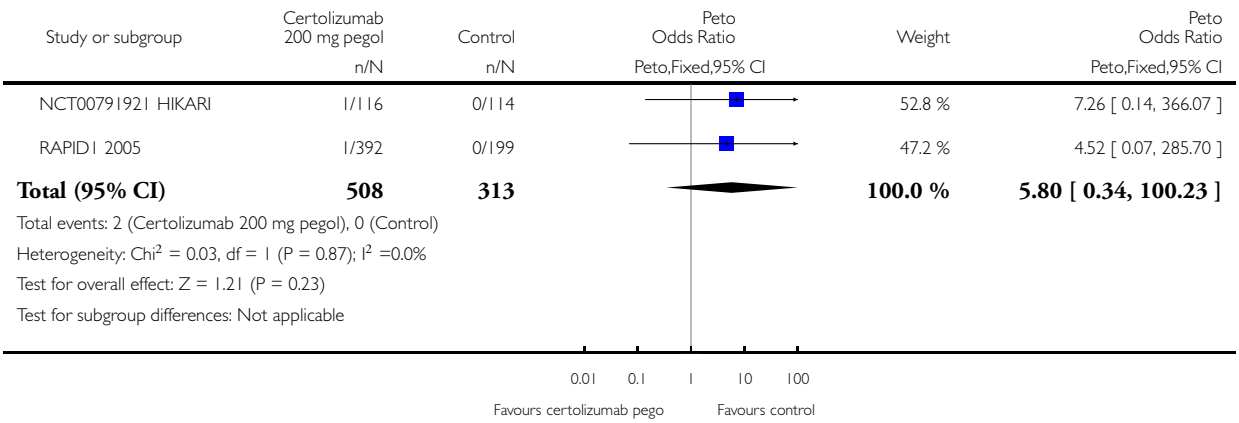


Analysis 8.30. Comparison 8 Safety, certolizumab 200 mg, Outcome 30 Herpes viral infection.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 30 Herpes viral infection

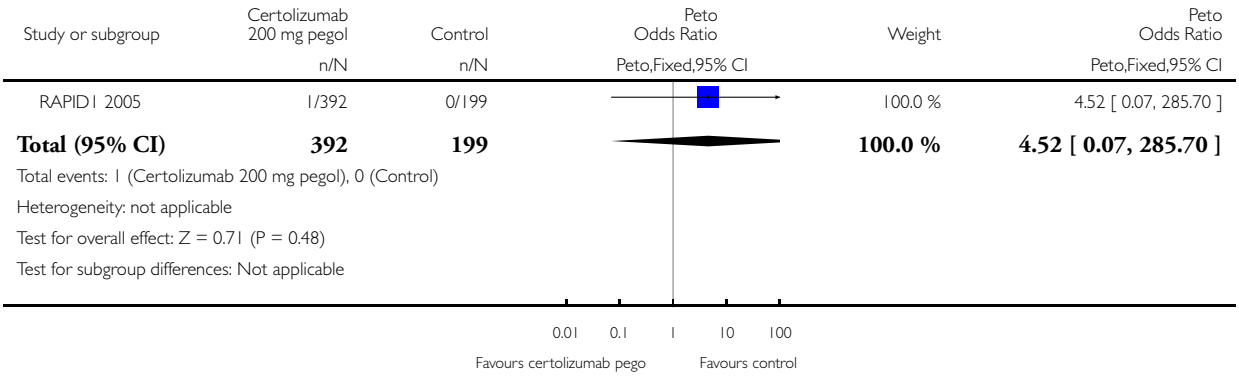


Analysis 8.31. Comparison 8 Safety, certolizumab 200 mg, Outcome 31 Bacterial peritonitis.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 31 Bacterial peritonitis

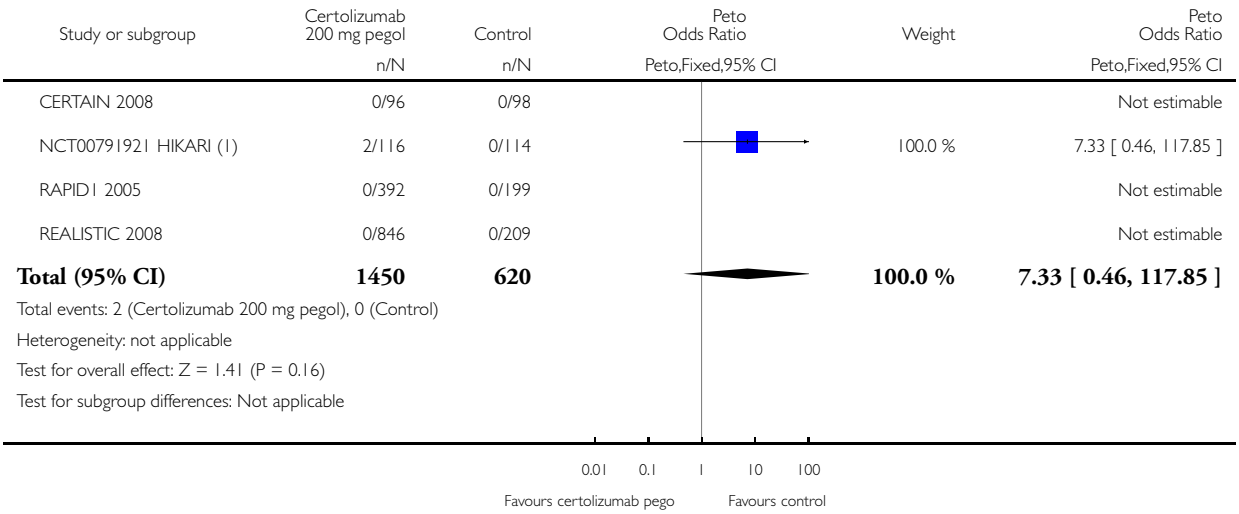


Analysis 8.32. Comparison 8 Safety, certolizumab 200 mg, Outcome 32 Opportunistic infections.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 32 Opportunistic infections



(1) 2 (1 Herpes Zoster and 1pneumocystis jirobenzi pneumonia)

Analysis 8.33. Comparison 8 Safety, certolizumab 200 mg, Outcome 33 Infections and infestations.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 33 Infections and infestations

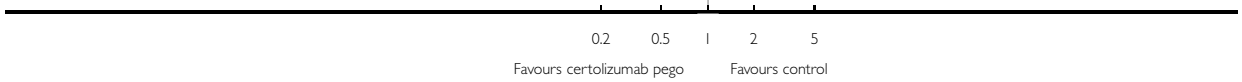
Study or subgroup	Certolizumab 200 mg pegol n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
CERTAIN 2008	27/96	26/98		11.8 %	1.06 [0.67, 1.68]
NCT00791921 HIKARI	33/116	27/114		12.6 %	1.20 [0.78, 1.86]
NCT00791999 JRAPID	27/82	16/77		9.5 %	1.58 [0.93, 2.70]
NCT00993317	30/85	9/42		7.0 %	1.65 [0.86, 3.14]
RAPID1 2005	171/392	52/199		22.6 %	1.67 [1.29, 2.16]
RAPID2 2007	26/108	69/248		14.7 %	0.87 [0.59, 1.28]
REALISTIC 2008	245/846	48/209		21.8 %	1.26 [0.96, 1.65]
Total (95% CI)	**1725**	**987**		**100.0 %**	**1.29 [1.07, 1.56]**

Total events: 559 (Certolizumab 200 mg pegol), 247 (Control)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 9.71$, df = 6 (P = 0.14); $I^2 = 38\%$

Test for overall effect: Z = 2.63 (P = 0.0085)

Test for subgroup differences: Not applicable



Analysis 8.34. Comparison 8 Safety, certolizumab 200 mg, Outcome 34 Gastroenteritis.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 34 Gastroenteritis

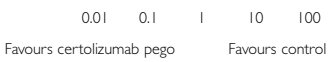
Study or subgroup	Certolizumab 200 mg pegol n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CERTAIN 2008	7/96	6/98		93.2 %	1.20 [0.39, 3.70]
RAPID1 2005	0/392	1/199		6.8 %	0.05 [0.00, 3.25]
Total (95% CI)	**488**	**297**		**100.0 %**	**0.97 [0.33, 2.87]**

Total events: 7 (Certolizumab 200 mg pegol), 7 (Control)

Heterogeneity: $Chi^2 = 2.07$, df = 1 (P = 0.15); $I^2 = 52\%$

Test for overall effect: Z = 0.05 (P = 0.96)

Test for subgroup differences: Not applicable



Analysis 8.35. Comparison 8 Safety, certolizumab 200 mg, Outcome 35 Hematologic abnormalities.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 35 Hematologic abnormalities

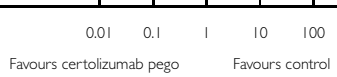
Study or subgroup	Certolizumab 200 mg pegol n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
NCT00791921 HIKARI	1/116	1/114		52.7 %	0.98 [0.06, 15.81]
RAPID1 2005	2/392	0/199		47.3 %	4.53 [0.24, 85.22]
Total (95% CI)	**508**	**313**		**100.0 %**	**2.02 [0.27, 15.21]**

Total events: 3 (Certolizumab 200 mg pegol), 1 (Control)

Heterogeneity: $Chi^2 = 0.55$, df = 1 (P = 0.46); $I^2 = 0.0\%$

Test for overall effect: Z = 0.68 (P = 0.49)

Test for subgroup differences: Not applicable



Analysis 8.36. Comparison 8 Safety, certolizumab 200 mg, Outcome 36 Decreased haemoglobin.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 36 Decreased haemoglobin

Study or subgroup	Certolizumab 200 mg pegol n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID1 2005	2/392	1/199		100.0 %	1.02 [0.09, 11.18]
Total (95% CI)	**392**	**199**		**100.0 %**	**1.02 [0.09, 11.18]**

Total events: 2 (Certolizumab 200 mg pegol), 1 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.01 (P = 0.99)

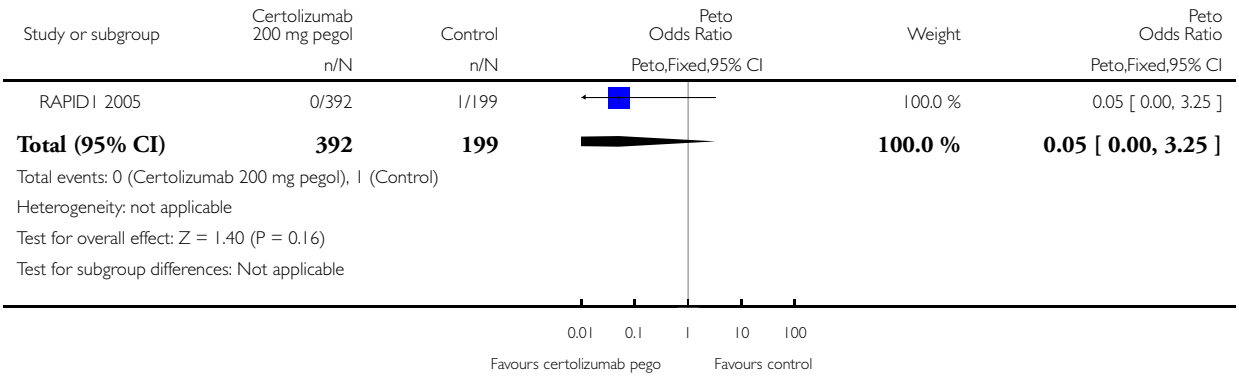
Test for subgroup differences: Not applicable

Analysis 8.37. Comparison 8 Safety, certolizumab 200 mg, Outcome 37 Increased platelet count.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 37 Increased platelet count

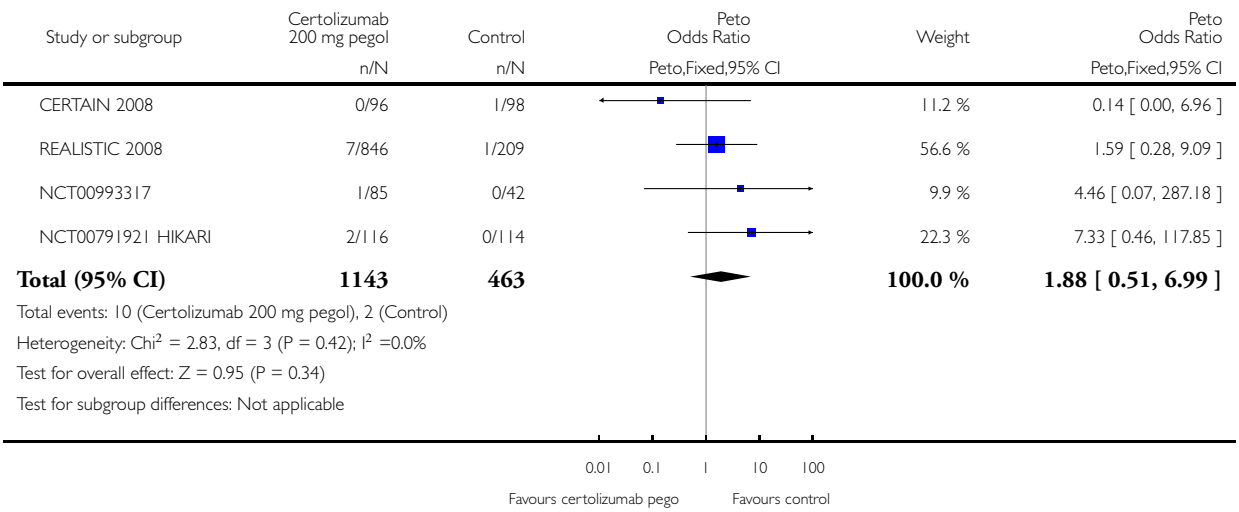


Analysis 8.38. Comparison 8 Safety, certolizumab 200 mg, Outcome 38 Pneumonia.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 38 Pneumonia



Analysis 8.39. Comparison 8 Safety, certolizumab 200 mg, Outcome 39 Diarrhoea.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 39 Diarrhoea

Study or subgroup	Certolizumab 200 mg pegol n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CERTAIN 2008	5/96	6/98		80.0 %	0.84 [0.25, 2.84]
NCT00993317	1/85	2/42		20.0 %	0.21 [0.02, 2.42]
Total (95% CI)	**181**	**140**		**100.0 %**	**0.64 [0.22, 1.90]**

Total events: 6 (Certolizumab 200 mg pegol), 8 (Control)

Heterogeneity: $Chi^2 = 0.98$, df = 1 (P = 0.32); $I^2 = 0.0\%$

Test for overall effect: Z = 0.80 (P = 0.42)

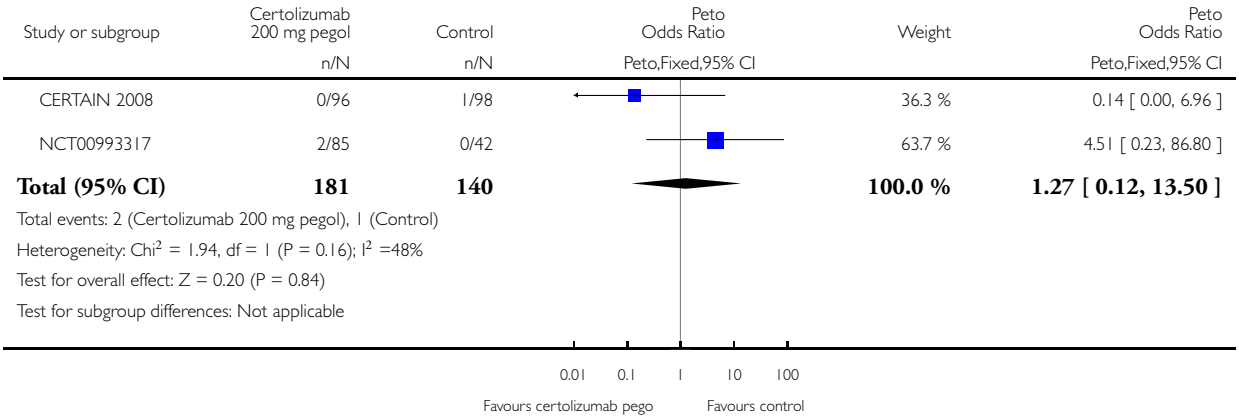
Test for subgroup differences: Not applicable

Analysis 8.40. Comparison 8 Safety, certolizumab 200 mg, Outcome 40 Cerebral haemorrhage including subarachnoid.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 40 Cerebral haemorrhage including subarachnoid

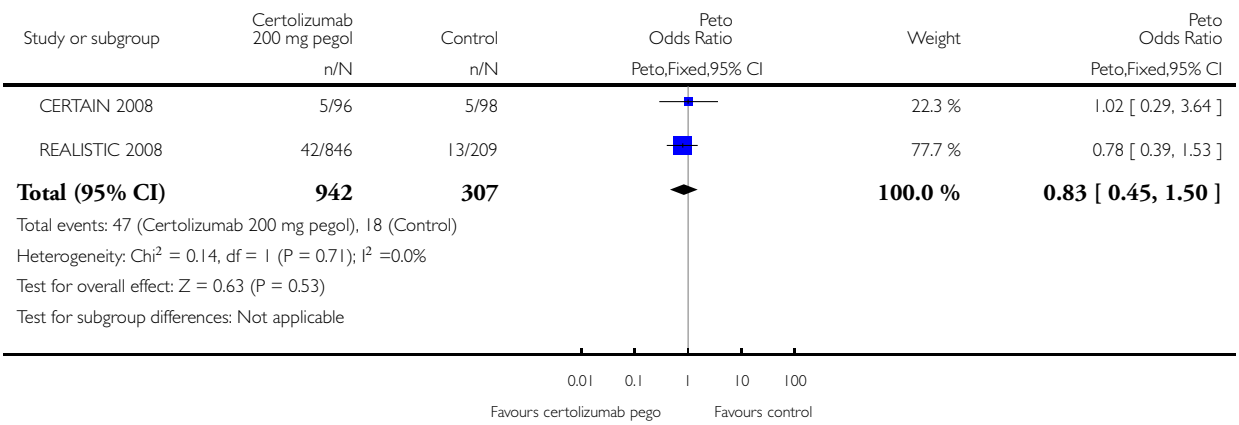


Analysis 8.41. Comparison 8 Safety, certolizumab 200 mg, Outcome 41 Nausea/vomiting.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 41 Nausea/vomiting



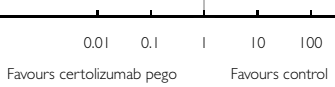
Analysis 8.42. Comparison 8 Safety, certolizumab 200 mg, Outcome 42 Acute miocardial infarction.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 42 Acute miocardial infarction

Study or subgroup	Certolizumab 200 mg pegol n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CERTAIN 2008	0/96	0/98			Not estimable
Total (95% CI)	**96**	**98**			**Not estimable**
Total events: 0 (Certolizumab 200 mg pegol), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					

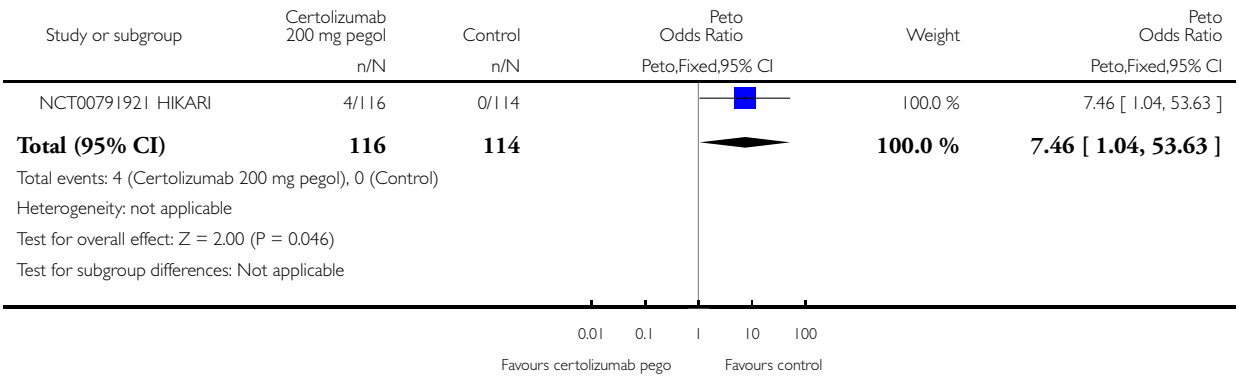


Analysis 8.43. Comparison 8 Safety, certolizumab 200 mg, Outcome 43 Constipation.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 43 Constipation

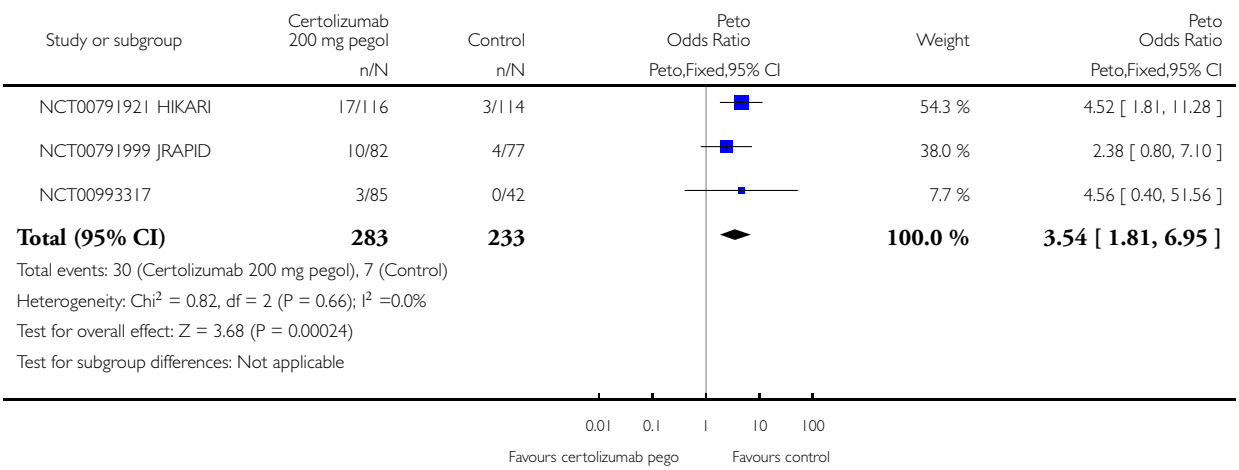


Analysis 8.44. Comparison 8 Safety, certolizumab 200 mg, Outcome 44 Skin and subcutaneous tissue disorders.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 44 Skin and subcutaneous tissue disorders



Analysis 8.45. Comparison 8 Safety, certolizumab 200 mg, Outcome 45 Cough.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 45 Cough

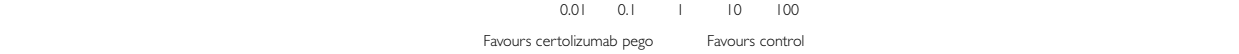
Study or subgroup	Certolizumab 200 mg pegol n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
NCT00993317	4/85	1/42		100.0 %	1.84 [0.28, 12.22]
Total (95% CI)	**85**	**42**		**100.0 %**	**1.84 [0.28, 12.22]**

Total events: 4 (Certolizumab 200 mg pegol), 1 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.63 (P = 0.53)

Test for subgroup differences: Not applicable

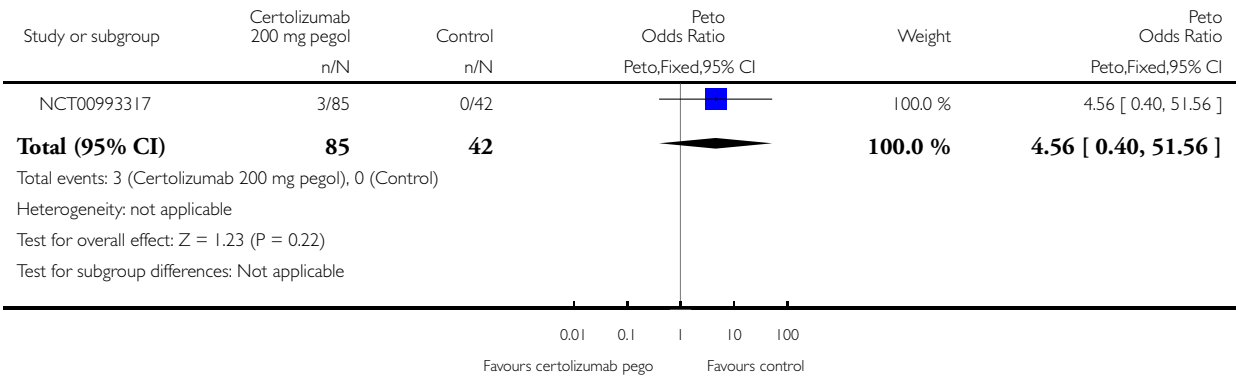


Analysis 8.46. Comparison 8 Safety, certolizumab 200 mg, Outcome 46 Pruritus.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 46 Pruritus

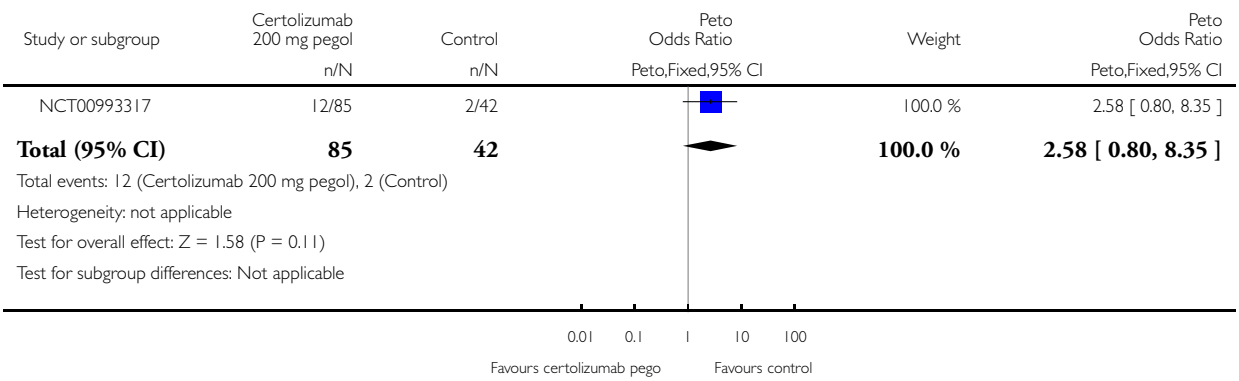


Analysis 8.47. Comparison 8 Safety, certolizumab 200 mg, Outcome 47 Abdominal pain/discomfort/dyspepsia.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 47 Abdominal pain/discomfort/dyspepsia

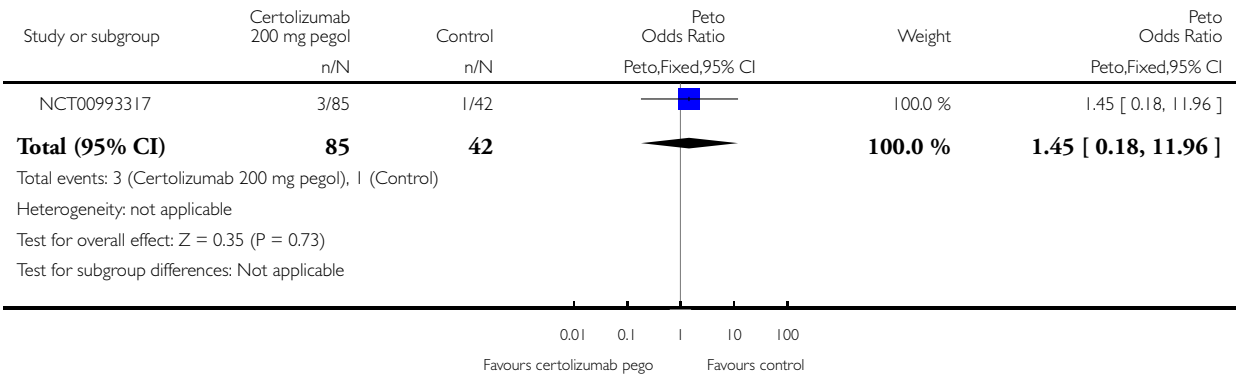


Analysis 8.48. Comparison 8 Safety, certolizumab 200 mg, Outcome 48 Fatigue.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 48 Fatigue

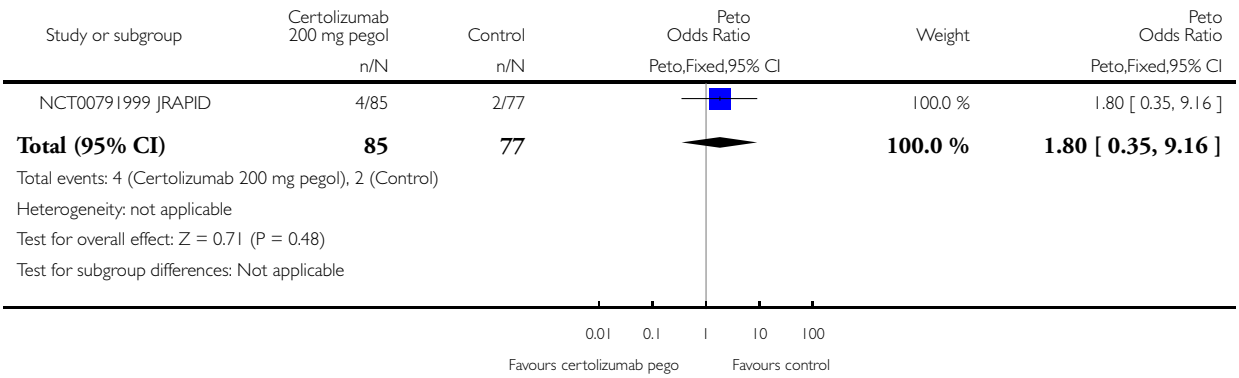


Analysis 8.49. Comparison 8 Safety, certolizumab 200 mg, Outcome 49 Periodontitis.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety, certolizumab 200 mg

Outcome: 49 Periodontitis



Analysis 9.1. Comparison 9 Safety, certolizumab 400 mg, Outcome 1 Any adverse events.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 1 Any adverse events

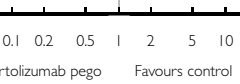
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
CDP870-014 2009	97/124	83/119		24.6 %	1.12 [0.96, 1.30]
FAST4WARD 2005	84/111	63/109		19.9 %	1.31 [1.08, 1.59]
NCT00791999 JRAPID	46/85	31/77		9.9 %	1.34 [0.96, 1.88]
RAPID1 2005	298/389	115/199		27.0 %	1.33 [1.16, 1.51]
RAPID2 2007	125/246	66/125		18.5 %	0.96 [0.78, 1.18]
Total (95% CI)	**955**	**629**		**100.0 %**	**1.20 [1.06, 1.35]**

Total events: 650 (Certolizumab pegol 400 mg), 358 (Control)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 8.60$, df = 4 (P = 0.07); $I^2 = 53\%$

Test for overall effect: Z = 2.89 (P = 0.0038)

Test for subgroup differences: Not applicable

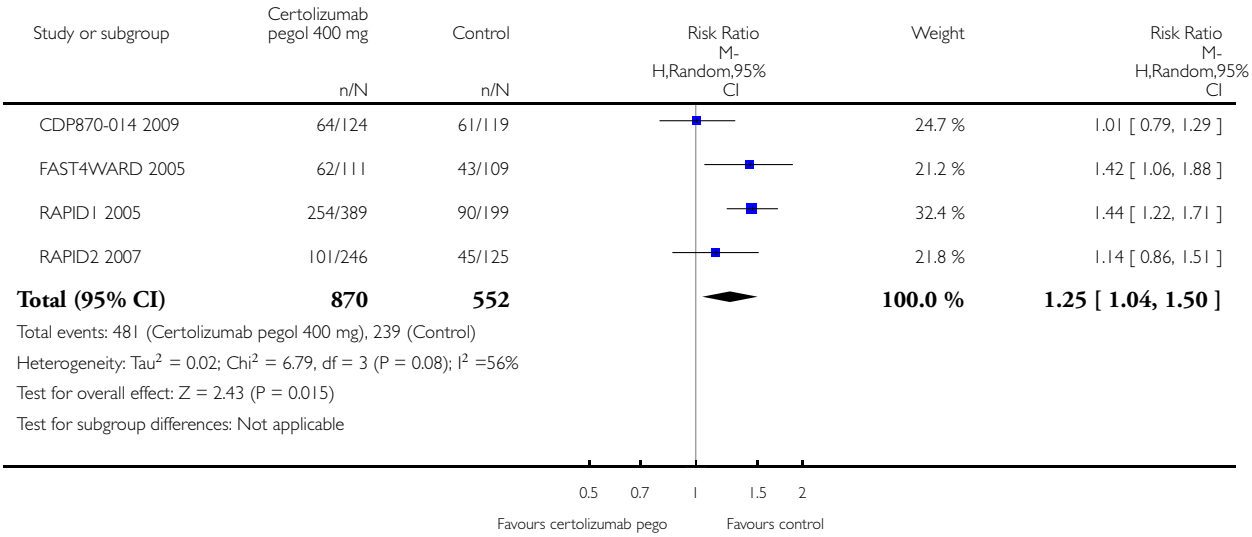


Analysis 9.2. Comparison 9 Safety, certolizumab 400 mg, Outcome 2 Adverse events Intensity mild.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 2 Adverse events Intensity mild



Analysis 9.3. Comparison 9 Safety, certolizumab 400 mg, Outcome 3 Adverse events Intensity moderate.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 3 Adverse events Intensity moderate

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
CDP870-014 2009	59/124	45/119		24.4 %	1.26 [0.94, 1.69]
FAST4WARD 2005	52/111	40/109		21.7 %	1.28 [0.93, 1.75]
RAPID1 2005	177/389	66/199		37.9 %	1.37 [1.10, 1.72]
RAPID2 2007	57/246	32/125		16.0 %	0.91 [0.62, 1.32]
Total (95% CI)	**870**	**552**		**100.0 %**	**1.24 [1.06, 1.45]**

Total events: 345 (Certolizumab pegol 400 mg), 183 (Control)

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.52$, df = 3 (P = 0.32); $I^2 = 15\%$

Test for overall effect: Z = 2.64 (P = 0.0082)

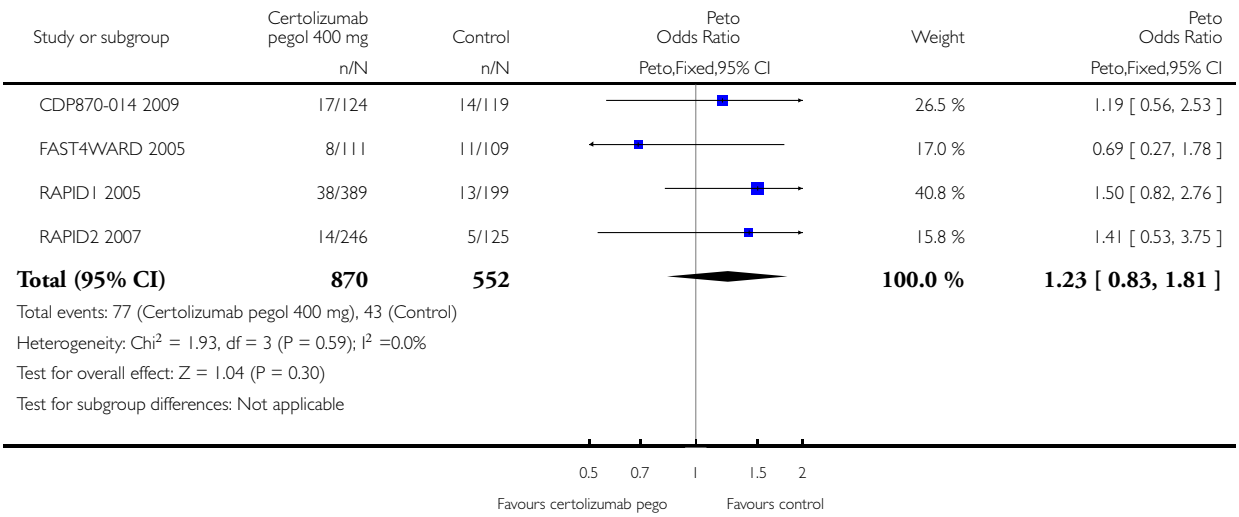
Test for subgroup differences: Not applicable

Analysis 9.4. Comparison 9 Safety, certolizumab 400 mg, Outcome 4 Adverse events Intensity severe.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 4 Adverse events Intensity severe



Analysis 9.5. Comparison 9 Safety, certolizumab 400 mg, Outcome 5 Adverse events related to study drug.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 5 Adverse events related to study drug

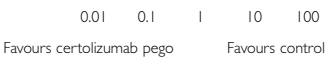
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
FAST4WARD 2005	27/111	24/109		20.0 %	1.10 [0.68, 1.79]
RAPID1 2005	166/389	50/199		54.7 %	1.70 [1.30, 2.22]
RAPID2 2007	56/246	23/125		25.2 %	1.24 [0.80, 1.91]
Total (95% CI)	**746**	**433**		**100.0 %**	**1.46 [1.19, 1.80]**

Total events: 249 (Certolizumab pegol 400 mg), 97 (Control)

Heterogeneity: Chi^2 = 3.08, df = 2 (P = 0.21); I^2 =35%

Test for overall effect: Z = 3.65 (P = 0.00027)

Test for subgroup differences: Not applicable

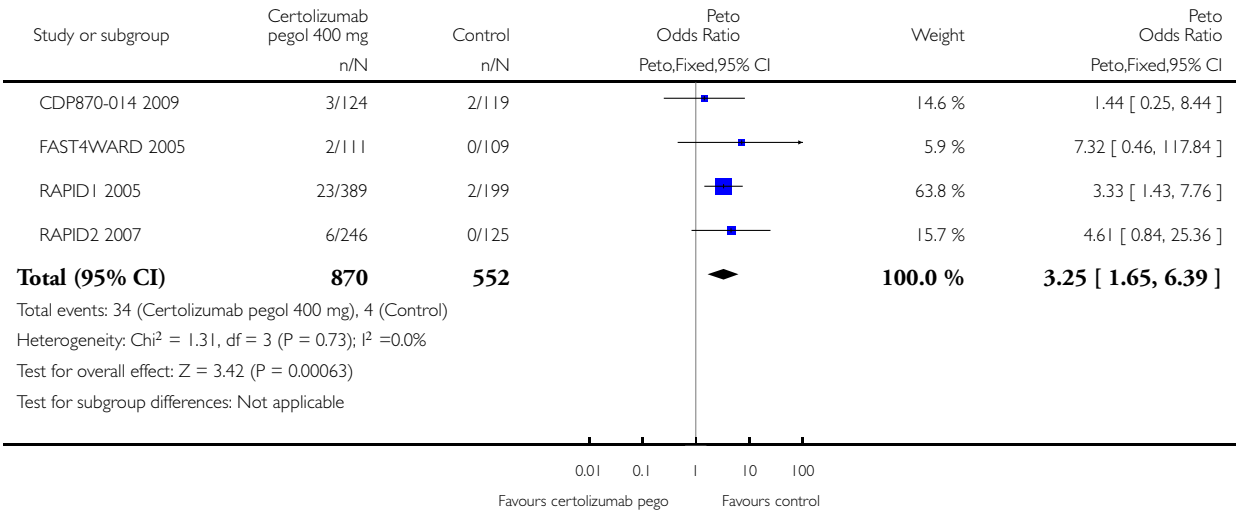


Analysis 9.6. Comparison 9 Safety, certolizumab 400 mg, Outcome 6 Serious infections.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 6 Serious infections



Analysis 9.7. Comparison 9 Safety, certolizumab 400 mg, Outcome 7 3Serious Adverse Events (SAE).

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 7 3Serious Adverse Events (SAE)

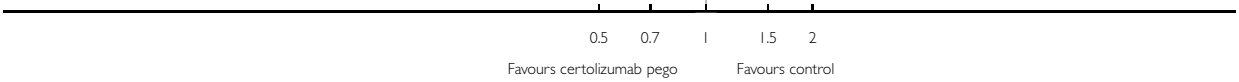
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CDP870-014 2009	16/124	12/119		23.2 %	1.32 [0.60, 2.89]
FAST4WARD 2005	8/111	3/109		9.8 %	2.54 [0.76, 8.53]
NCT00791999 JRAPID	5/85	1/77		5.4 %	3.59 [0.70, 18.26]
RAPID1 2005	48/389	11/199		44.4 %	2.12 [1.20, 3.75]
RAPID2 2007	18/246	4/125		17.3 %	2.09 [0.84, 5.19]
Total (95% CI)	**955**	**629**		**100.0 %**	**1.98 [1.36, 2.90]**

Total events: 95 (Certolizumab pegol 400 mg), 31 (Control)

Heterogeneity: $Chi^2 = 1.78$, df = 4 (P = 0.78); $I^2 = 0.0\%$

Test for overall effect: Z = 3.55 (P = 0.00038)

Test for subgroup differences: Not applicable



Analysis 9.8. Comparison 9 Safety, certolizumab 400 mg, Outcome 8 Adverse events leading to death.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 8 Adverse events leading to death

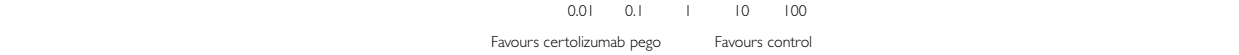
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
FAST4WARD 2005	0/111	0/109			Not estimable
RAPID1 2005	4/389	1/199		83.3 %	1.86 [0.29, 11.96]
RAPID2 2007	1/246	0/125		16.7 %	4.52 [0.07, 285.66]
Total (95% CI)	**746**	**433**		**100.0 %**	**2.16 [0.40, 11.79]**

Total events: 5 (Certolizumab pegol 400 mg), 1 (Control)

Heterogeneity: $Chi^2 = 0.15$, df = 1 (P = 0.70); $I^2 = 0.0\%$

Test for overall effect: Z = 0.89 (P = 0.37)

Test for subgroup differences: Not applicable



Analysis 9.9. Comparison 9 Safety, certolizumab 400 mg, Outcome 9 Adverse events leading to withdrawal.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 9 Adverse events leading to withdrawal

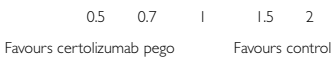
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CDP870-014 2009	7/124	6/119		21.3 %	1.13 [0.37, 3.44]
FAST4WARD 2005	5/111	2/109		11.8 %	2.37 [0.53, 10.64]
NCT00791999 JRAPID	7/85	3/77		16.3 %	2.11 [0.59, 7.55]
RAPID1 2005	22/389	3/199		37.1 %	2.77 [1.19, 6.44]
RAPID2 2007	7/246	2/125		13.6 %	1.69 [0.42, 6.84]
Total (95% CI)	**955**	**629**		**100.0 %**	**2.01 [1.20, 3.36]**

Total events: 48 (Certolizumab pegol 400 mg), 16 (Control)

Heterogeneity: $Chi^2 = 1.69$, $df = 4$ ($P = 0.79$); $I^2 = 0.0\%$

Test for overall effect: $Z = 2.65$ ($P = 0.0081$)

Test for subgroup differences: Not applicable



Analysis 9.10. Comparison 9 Safety, certolizumab 400 mg, Outcome 10 Death.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 10 Death

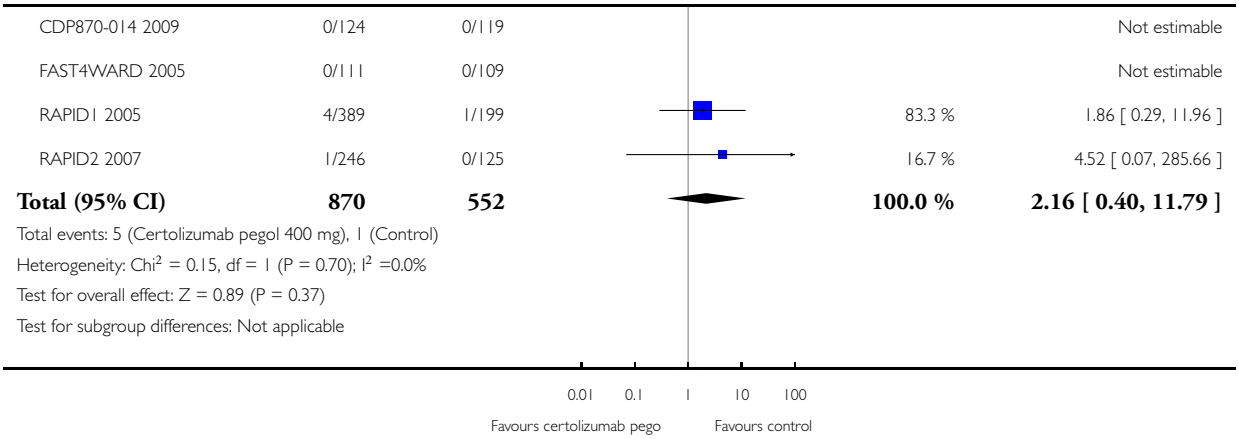
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CDP870-014 2009	0/124	0/119			Not estimable
FAST4WARD 2005	0/111	0/109			Not estimable
RAPID1 2005	4/389	1/199		83.3 %	1.86 [0.29, 11.96]
RAPID2 2007	1/246	0/125		16.7 %	4.52 [0.07, 285.66]
Total (95% CI)	**870**	**552**		**100.0 %**	**2.16 [0.40, 11.79]**

Total events: 5 (Certolizumab pegol 400 mg), 1 (Control)

Heterogeneity: $Chi^2 = 0.15$, df = 1 (P = 0.70); $I^2 = 0.0\%$

Test for overall effect: Z = 0.89 (P = 0.37)

Test for subgroup differences: Not applicable



Analysis 9.11. Comparison 9 Safety, certolizumab 400 mg, Outcome 11 Vomiting.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 11 Vomiting

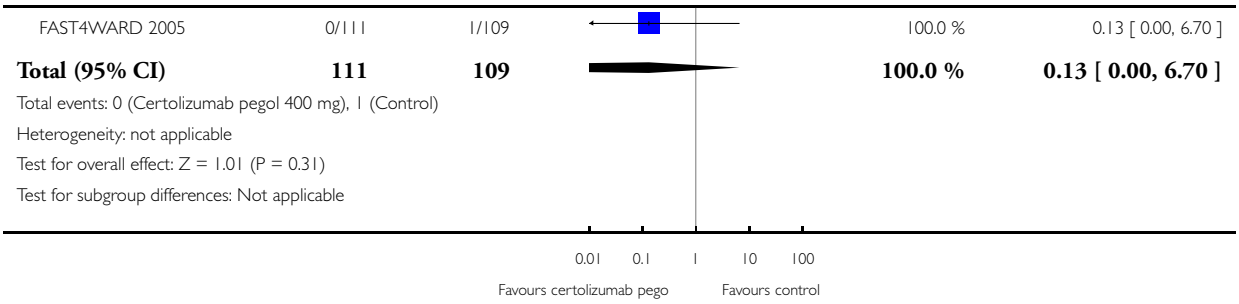
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
FAST4WARD 2005	0/111	1/109		100.0 %	0.13 [0.00, 6.70]
Total (95% CI)	**111**	**109**		**100.0 %**	**0.13 [0.00, 6.70]**

Total events: 0 (Certolizumab pegol 400 mg), 1 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.01 (P = 0.31)

Test for subgroup differences: Not applicable



Analysis 9.12. Comparison 9 Safety, certolizumab 400 mg, Outcome 12 Pneumonitis.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 12 Pneumonitis

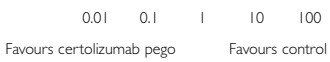
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
FAST4WARD 2005	0/111	1/109		100.0 %	0.13 [0.00, 6.70]
Total (95% CI)	**111**	**109**		**100.0 %**	**0.13 [0.00, 6.70]**

Total events: 0 (Certolizumab pegol 400 mg), 1 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.01 (P = 0.31)

Test for subgroup differences: Not applicable



Analysis 9.13. Comparison 9 Safety, certolizumab 400 mg, Outcome 13 Tuberculosis.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 13 Tuberculosis

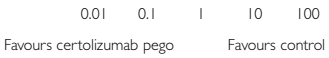
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
FAST4WARD 2005	0/111	0/109			Not estimable
RAPID1 2005	3/389	0/199		60.0 %	4.56 [0.42, 50.01]
RAPID2 2007	2/246	0/125		40.0 %	4.54 [0.24, 85.48]
Total (95% CI)	**746**	**433**		**100.0 %**	**4.55 [0.71, 29.11]**

Total events: 5 (Certolizumab pegol 400 mg), 0 (Control)

Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 1.60 (P = 0.11)

Test for subgroup differences: Not applicable



Analysis 9.14. Comparison 9 Safety, certolizumab 400 mg, Outcome 14 Arthritis bacterial.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 14 Arthritis bacterial

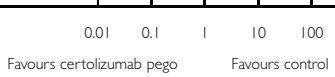
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
FAST4WARD 2005	1/111	0/109		100.0 %	7.26 [0.14, 365.79]
Total (95% CI)	**111**	**109**		**100.0 %**	**7.26 [0.14, 365.79]**

Total events: 1 (Certolizumab pegol 400 mg), 0 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.99 (P = 0.32)

Test for subgroup differences: Not applicable

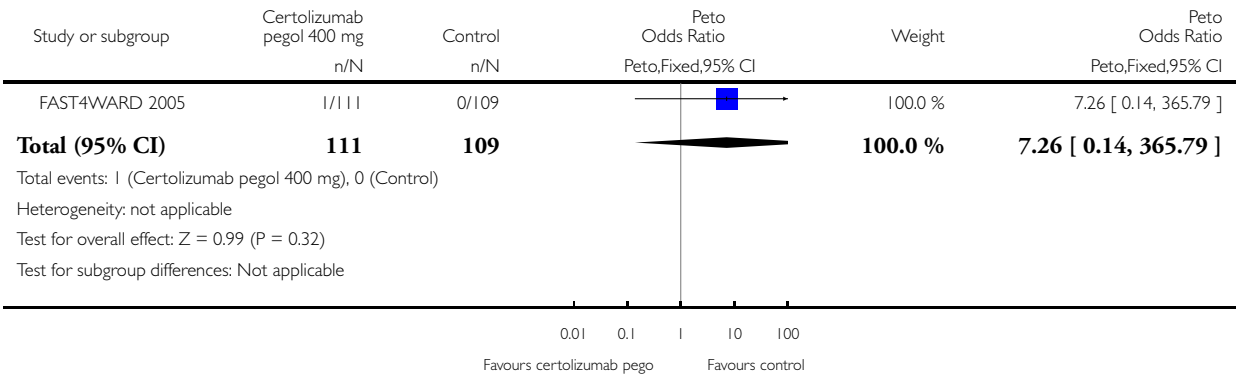


Analysis 9.15. Comparison 9 Safety, certolizumab 400 mg, Outcome 15 Mastitis.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 15 Mastitis

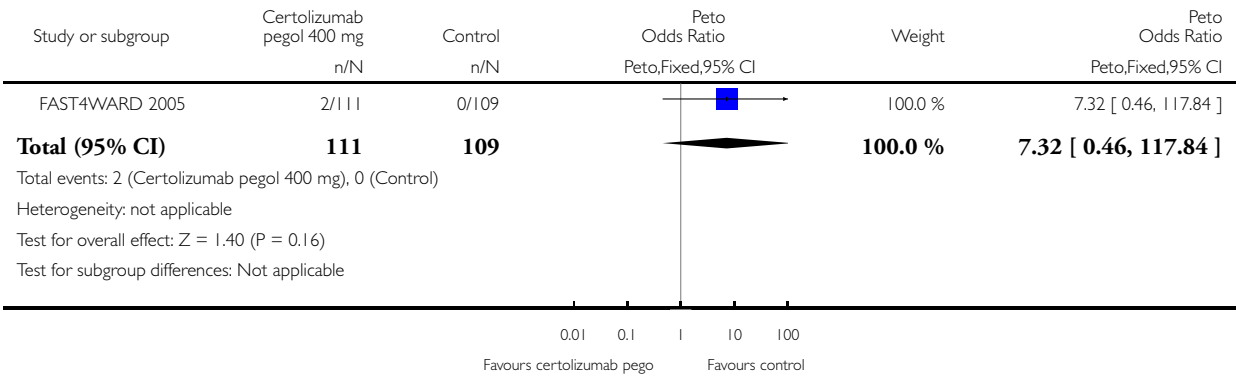


Analysis 9.16. Comparison 9 Safety, certolizumab 400 mg, Outcome 16 Benign Tumour.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 16 Benign Tumour

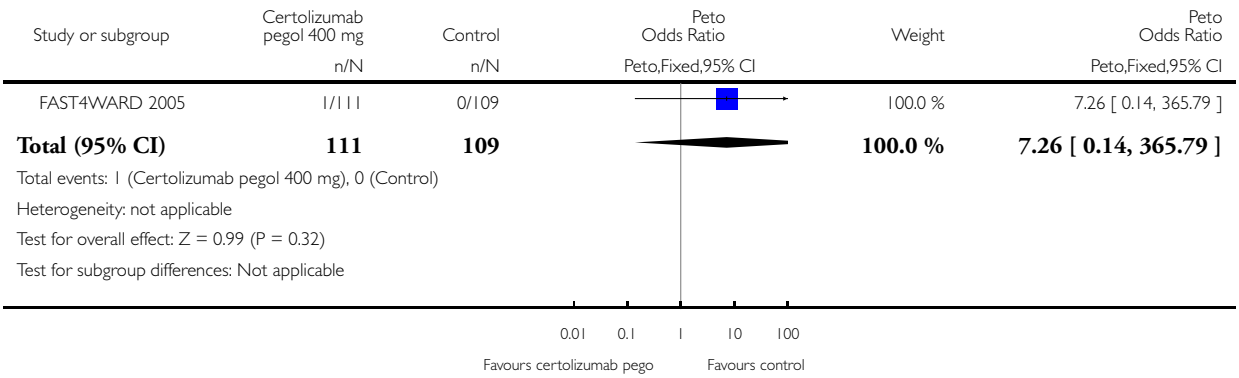


Analysis 9.17. Comparison 9 Safety, certolizumab 400 mg, Outcome 17 Ischaemeic stroke.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 17 Ischaemeic stroke

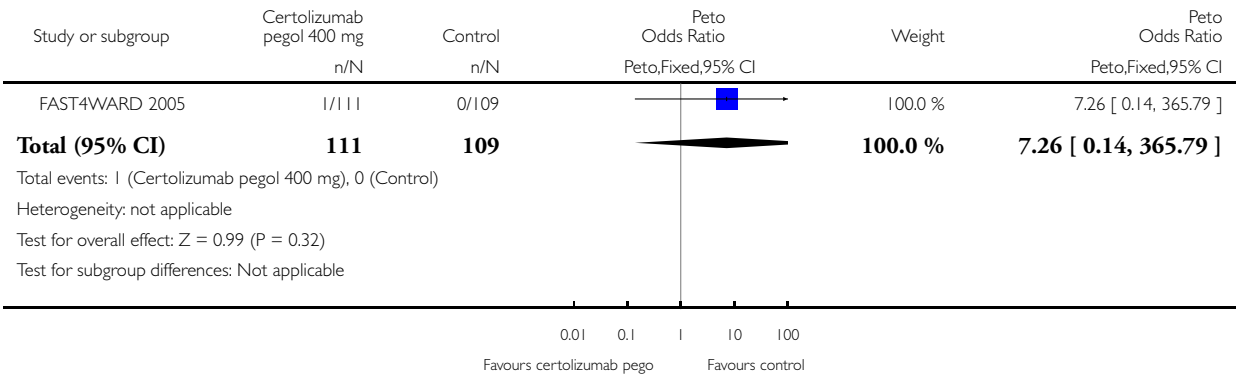


Analysis 9.18. Comparison 9 Safety, certolizumab 400 mg, Outcome 18 Dizziness postural.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 18 Dizziness postural

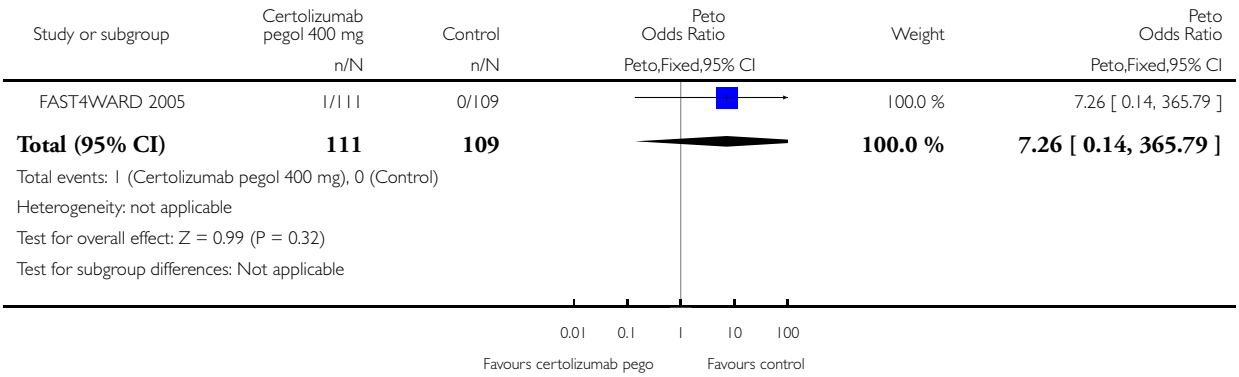


Analysis 9.19. Comparison 9 Safety, certolizumab 400 mg, Outcome 19 Menorrhagia.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 19 Menorrhagia



Analysis 9.20. Comparison 9 Safety, certolizumab 400 mg, Outcome 20 Malignancies included lymphoma.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 20 Malignancies included lymphoma

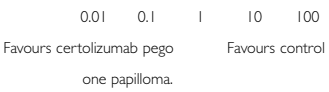
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
FAST4WARD 2005	0/111	0/109			Not estimable
RAPID1 2005 (1)	4/389	1/199		71.4 %	1.86 [0.29, 11.96]
RAPID2 2007 (2)	1/246	1/125		28.6 %	0.48 [0.03, 9.06]
Total (95% CI)	**746**	**433**		**100.0 %**	**1.26 [0.26, 6.08]**

Total events: 5 (Certolizumab pegol 400 mg), 2 (Control)

Heterogeneity: $Chi^2 = 0.58$, df = 1 (P = 0.44); $I^2 = 0.0\%$

Test for overall effect: Z = 0.29 (P = 0.77)

Test for subgroup differences: Not applicable



one papilloma.

(1) In the placebo arm one patient suffered a thyroid neoplasm and 4 in the certolizumab 400 mg sc suffered two tongue neoplasm, 1 extranodal marginal zone B cell limphoma and

(2) One case of malignant neoplasm was reported in each arm, namely bladder cancer in the placebo group and colon cancer in certolizumab pegol 400 mg group

Analysis 9.21. Comparison 9 Safety, certolizumab 400 mg, Outcome 21 Injection site pain.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 21 Injection site pain

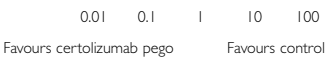
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
FAST4WARD 2005	0/111	2/109		27.2 %	0.13 [0.01, 2.12]
RAPID1 2005	5/389	0/199		60.7 %	4.58 [0.71, 29.39]
RAPID2 2007	1/246	0/125		12.2 %	4.52 [0.07, 285.66]
Total (95% CI)	**746**	**433**		**100.0 %**	**1.74 [0.41, 7.42]**

Total events: 6 (Certolizumab pegol 400 mg), 2 (Control)

Heterogeneity: $Chi^2 = 4.56$, df = 2 (P = 0.10); $I^2 = 56\%$

Test for overall effect: Z = 0.75 (P = 0.45)

Test for subgroup differences: Not applicable



Analysis 9.22. Comparison 9 Safety, certolizumab 400 mg, Outcome 22 Injection side reactions.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 22 Injection side reactions

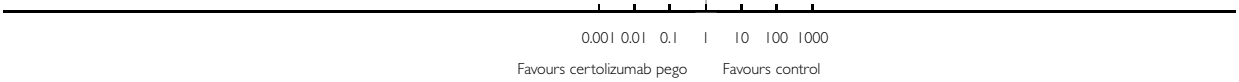
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CDP870-014 2009 (1)	5/124	34/119		54.6 %	0.16 [0.08, 0.32]
FAST4WARD 2005	5/111	15/109		30.3 %	0.33 [0.13, 0.82]
NCT00791999 JRAPID	2/85	0/77		3.3 %	6.81 [0.42, 110.13]
RAPID1 2005	3/389	0/199		4.4 %	4.56 [0.42, 50.01]
RAPID2 2007	5/246	0/125		7.3 %	4.59 [0.71, 29.64]
Total (95% CI)	**955**	**629**		**100.0 %**	**0.34 [0.20, 0.56]**

Total events: 20 (Certolizumab pegol 400 mg), 49 (Control)

Heterogeneity: $Chi^2 = 20.89$, df = 4 (P = 0.00033); $I^2 = 81\%$

Test for overall effect: Z = 4.21 (P = 0.000025)

Test for subgroup differences: Not applicable



(1) Authors explained that "possibly due to the use of the sorbitol placebo"

Analysis 9.23. Comparison 9 Safety, certolizumab 400 mg, Outcome 23 Anti-certolizumab pegol antibodies.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 23 Anti-certolizumab pegol antibodies

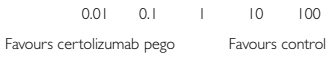
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
FAST4WARD 2005	9/111	0/109		71.0 %	7.82 [2.07, 29.62]
RAPID2 2007	4/246	0/125		29.0 %	4.57 [0.57, 36.68]
Total (95% CI)	**357**	**234**		**100.0 %**	**6.70 [2.18, 20.55]**

Total events: 13 (Certolizumab pegol 400 mg), 0 (Control)

Heterogeneity: $Chi^2 = 0.18$, df = 1 (P = 0.67); $I^2 = 0.0\%$

Test for overall effect: Z = 3.32 (P = 0.00089)

Test for subgroup differences: Not applicable



Analysis 9.24. Comparison 9 Safety, certolizumab 400 mg, Outcome 24 Antinuclear antibodies (ANA).

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 24 Antinuclear antibodies (ANA)

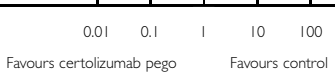
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
FAST4WARD 2005	19/111	12/109		100.0 %	1.65 [0.77, 3.53]
Total (95% CI)	**111**	**109**		**100.0 %**	**1.65 [0.77, 3.53]**

Total events: 19 (Certolizumab pegol 400 mg), 12 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.30 (P = 0.19)

Test for subgroup differences: Not applicable



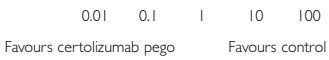
Analysis 9.25. Comparison 9 Safety, certolizumab 400 mg, Outcome 25 Prolonged activated partial thromboplastin time (aPTT).

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 25 Prolonged activated partial thromboplastin time (aPTT)

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID2 2007	12/246	2/125		100.0 %	2.46 [0.80, 7.60]
Total (95% CI)	**246**	**125**		**100.0 %**	**2.46 [0.80, 7.60]**
Total events: 12 (Certolizumab pegol 400 mg), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.56 (P = 0.12)					
Test for subgroup differences: Not applicable					



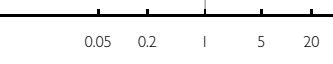
Analysis 9.26. Comparison 9 Safety, certolizumab 400 mg, Outcome 26 Urinary tract infection.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 26 Urinary tract infection

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID1 2005	33/389	13/199		75.9 %	1.31 [0.69, 2.47]
RAPID2 2007	5/246	9/125		24.1 %	0.24 [0.08, 0.75]
Total (95% CI)	**635**	**324**		**100.0 %**	**0.87 [0.50, 1.52]**
Total events: 38 (Certolizumab pegol 400 mg), 22 (Control)					
Heterogeneity: Chi^2 = 6.54, df = 1 (P = 0.01); I^2 =85%					
Test for overall effect: Z = 0.48 (P = 0.63)					
Test for subgroup differences: Not applicable					



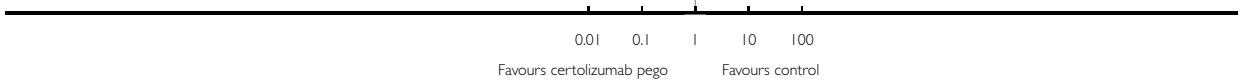
Analysis 9.27. Comparison 9 Safety, certolizumab 400 mg, Outcome 27 Back pain.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 27 Back pain

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CDP870-014 2009	7/124	2/119		31.4 %	3.03 [0.80, 11.43]
RAPID1 2005	20/389	2/199		68.6 %	3.15 [1.28, 7.74]
Total (95% CI)	**513**	**318**		**100.0 %**	**3.11 [1.48, 6.55]**
Total events: 27 (Certolizumab pegol 400 mg), 4 (Control)					
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.96); I^2 =0.0%					
Test for overall effect: Z = 2.98 (P = 0.0028)					
Test for subgroup differences: Not applicable					



Analysis 9.28. Comparison 9 Safety, certolizumab 400 mg, Outcome 28 Upper respiratory tract infection.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 28 Upper respiratory tract infection

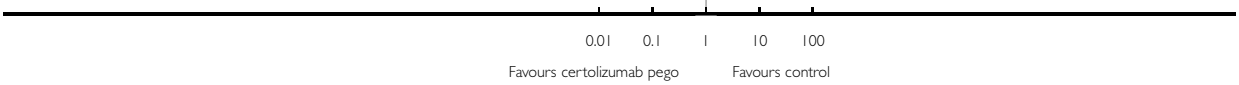
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CDP870-014 2009	4/124	4/119		18.9 %	0.96 [0.23, 3.91]
NCT00791999 JRAPID	3/85	3/77		14.1 %	0.90 [0.18, 4.60]
RAPID1 2005	21/389	5/199		54.2 %	1.98 [0.86, 4.54]
RAPID2 2007	4/246	2/125		12.9 %	1.02 [0.18, 5.59]
Total (95% CI)	**844**	**520**		**100.0 %**	**1.42 [0.77, 2.61]**

Total events: 32 (Certolizumab pegol 400 mg), 14 (Control)

Heterogeneity: $Chi^2 = 1.36$, df = 3 (P = 0.72); $I^2 = 0.0\%$

Test for overall effect: Z = 1.12 (P = 0.26)

Test for subgroup differences: Not applicable



Analysis 9.29. Comparison 9 Safety, certolizumab 400 mg, Outcome 29 Lower respiratory tract infection/ lung infection.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 29 Lower respiratory tract infection/ lung infection

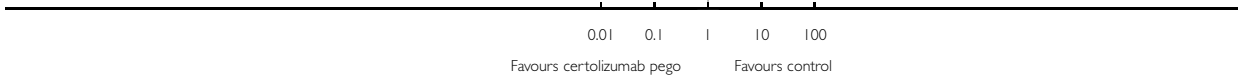
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CDP870-014 2009	3/124	3/119		41.1 %	0.96 [0.19, 4.83]
NCT00791999 JRAPID	4/85	1/77		34.0 %	3.10 [0.52, 18.35]
RAPID1 2005	4/389	0/199		24.9 %	4.57 [0.57, 36.44]
Total (95% CI)	**598**	**395**		**100.0 %**	**2.11 [0.75, 5.95]**

Total events: 11 (Certolizumab pegol 400 mg), 4 (Control)

Heterogeneity: $Chi^2 = 1.63$, df = 2 (P = 0.44); $I^2 = 0.0\%$

Test for overall effect: Z = 1.41 (P = 0.16)

Test for subgroup differences: Not applicable



Analysis 9.30. Comparison 9 Safety, certolizumab 400 mg, Outcome 30 Headache.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 30 Headache

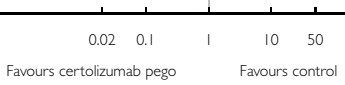
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CDP870-014 2009	12/124	9/119		35.1 %	1.31 [0.53, 3.19]
NCT00791999 JRAPID	3/85	0/77		5.4 %	6.89 [0.70, 67.36]
RAPID1 2005	18/389	11/199		45.1 %	0.83 [0.38, 1.82]
RAPID2 2007	8/246	1/125		14.4 %	2.81 [0.69, 11.36]
Total (95% CI)	**844**	**520**		**100.0 %**	**1.30 [0.76, 2.20]**

Total events: 41 (Certolizumab pegol 400 mg), 21 (Control)

Heterogeneity: $Chi^2 = 4.50$, df = 3 (P = 0.21); $I^2 = 33\%$

Test for overall effect: Z = 0.96 (P = 0.34)

Test for subgroup differences: Not applicable



Analysis 9.31. Comparison 9 Safety, certolizumab 400 mg, Outcome 31 Bacteriuria.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 31 Bacteriuria

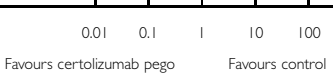
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID2 2007	6/246	4/125		100.0 %	0.75 [0.20, 2.82]
Total (95% CI)	**246**	**125**		**100.0 %**	**0.75 [0.20, 2.82]**

Total events: 6 (Certolizumab pegol 400 mg), 4 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.43 (P = 0.67)

Test for subgroup differences: Not applicable



Analysis 9.32. Comparison 9 Safety, certolizumab 400 mg, Outcome 32 Hypertension.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 32 Hypertension

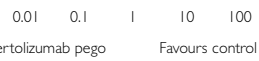
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
NCT00791999 JRAPID	2/85	0/77		4.9 %	6.81 [0.42, 110.13]
RAPID1 2005	32/389	2/199		71.3 %	3.76 [1.81, 7.80]
RAPID2 2007	9/246	2/125		23.7 %	2.04 [0.57, 7.25]
Total (95% CI)	**720**	**401**		**100.0 %**	**3.35 [1.80, 6.20]**

Total events: 43 (Certolizumab pegol 400 mg), 4 (Control)

Heterogeneity: $Chi^2 = 0.93$, df = 2 (P = 0.63); $I^2 = 0.0\%$

Test for overall effect: Z = 3.83 (P = 0.00013)

Test for subgroup differences: Not applicable

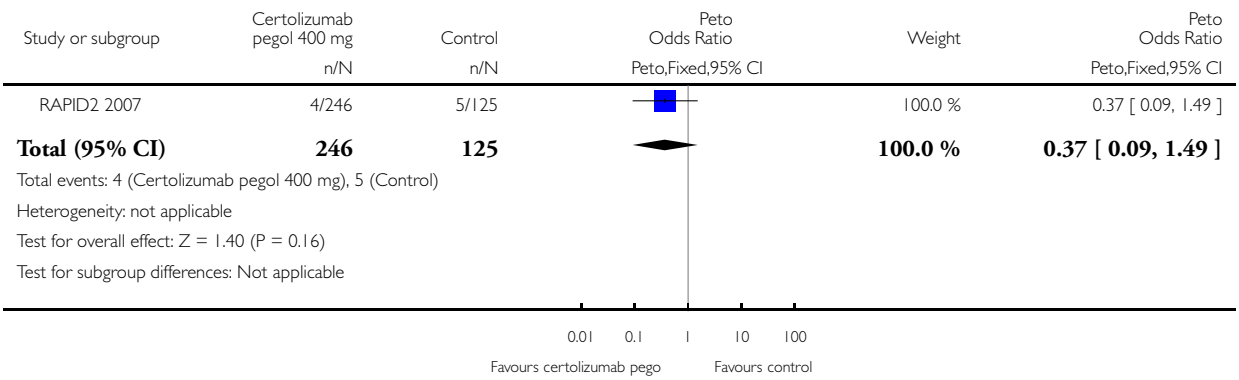


Analysis 9.33. Comparison 9 Safety, certolizumab 400 mg, Outcome 33 Hematuria.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 33 Hematuria

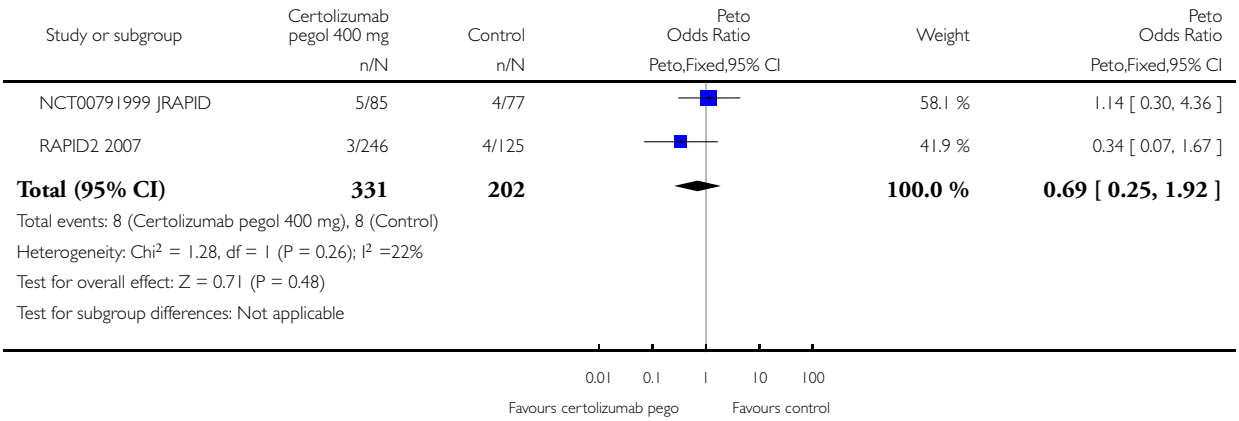


Analysis 9.34. Comparison 9 Safety, certolizumab 400 mg, Outcome 34 Hepatic enzyme increased.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 34 Hepatic enzyme increased

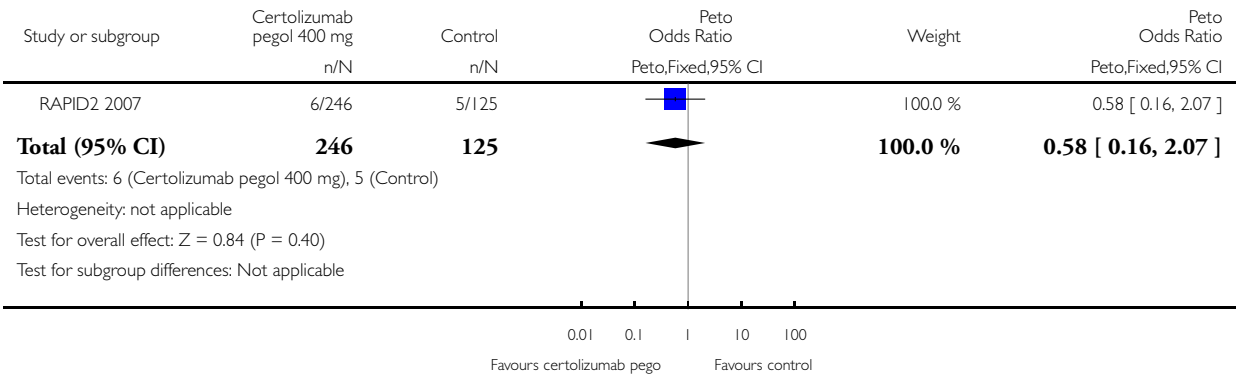


Analysis 9.35. Comparison 9 Safety, certolizumab 400 mg, Outcome 35 AST increased.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 35 AST increased

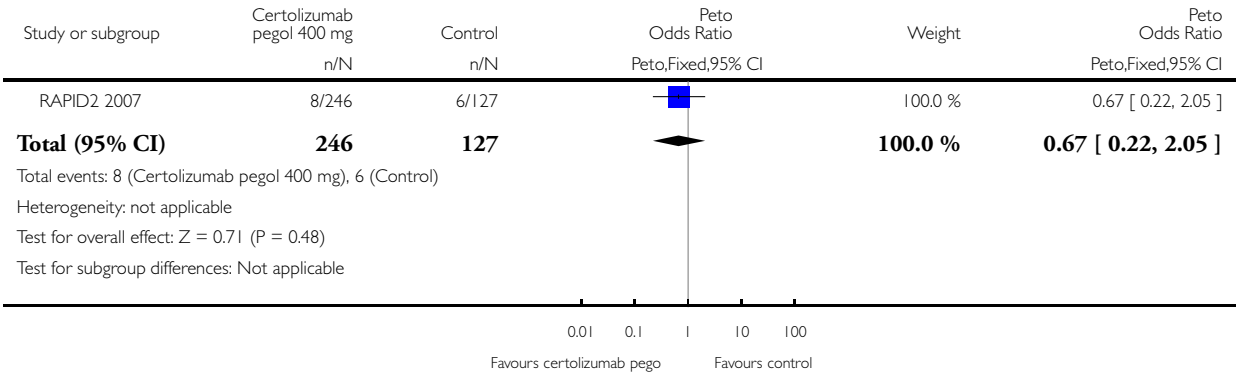


Analysis 9.36. Comparison 9 Safety, certolizumab 400 mg, Outcome 36 ALT increased.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 36 ALT increased

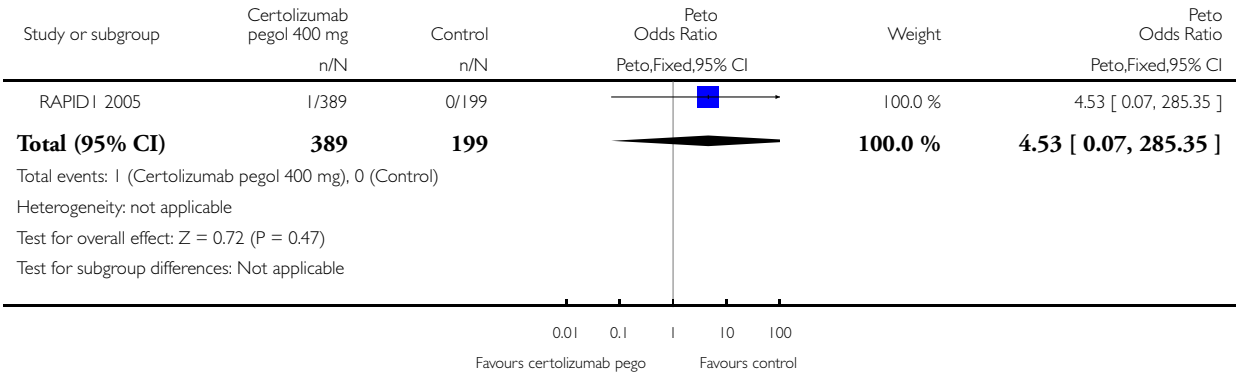


Analysis 9.37. Comparison 9 Safety, certolizumab 400 mg, Outcome 37 Herpes viral infection.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 37 Herpes viral infection

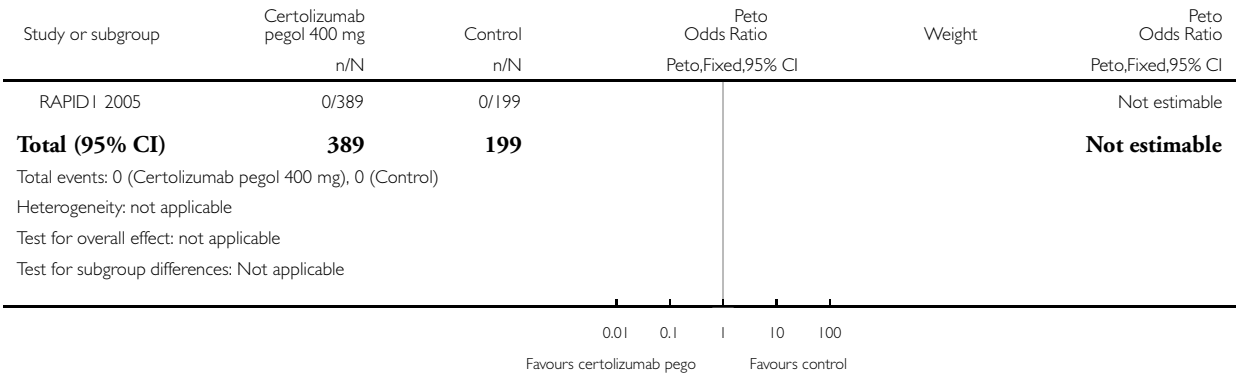


Analysis 9.38. Comparison 9 Safety, certolizumab 400 mg, Outcome 38 Bacterial peritonitis.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 38 Bacterial peritonitis



Analysis 9.39. Comparison 9 Safety, certolizumab 400 mg, Outcome 39 Opportunistic infections.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 39 Opportunistic infections

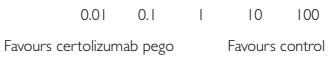
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID1 2005	0/389	0/199			Not estimable
Total (95% CI)	**389**	**199**			**Not estimable**

Total events: 0 (Certolizumab pegol 400 mg), 0 (Control)

Heterogeneity: not applicable

Test for overall effect: not applicable

Test for subgroup differences: Not applicable



Analysis 9.40. Comparison 9 Safety, certolizumab 400 mg, Outcome 40 Infections and infestations.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 40 Infections and infestations

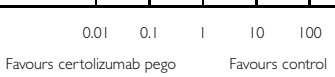
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
CDP870-014 2009	33/124	17/119		19.3 %	1.86 [1.10, 3.16]
NCT00791999 JRAPID	23/85	16/77		18.0 %	1.30 [0.74, 2.28]
RAPID1 2005	184/389	52/199		37.4 %	1.81 [1.40, 2.34]
RAPID2 2007	53/246	26/125		25.3 %	1.04 [0.68, 1.57]
Total (95% CI)	**844**	**520**		**100.0 %**	**1.49 [1.11, 1.99]**

Total events: 293 (Certolizumab pegol 400 mg), 111 (Control)

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 5.84$, df = 3 (P = 0.12); $I^2 = 49\%$

Test for overall effect: Z = 2.67 (P = 0.0076)

Test for subgroup differences: Not applicable



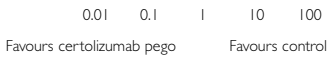
Analysis 9.41. Comparison 9 Safety, certolizumab 400 mg, Outcome 41 Nasopharyngitis/Pharyngitis.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 41 Nasopharyngitis/Pharyngitis

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CDP870-014 2009	15/124	8/119		27.6 %	1.87 [0.79, 4.40]
NCT00791999 JRAPID	15/85	12/77		29.8 %	1.16 [0.51, 2.64]
RAPID1 2005	30/389	3/199		36.8 %	3.22 [1.53, 6.76]
RAPID2 2007	4/246	1/125		5.8 %	1.86 [0.29, 11.99]
Total (95% CI)	**844**	**520**		**100.0 %**	**1.98 [1.26, 3.11]**
Total events: 64 (Certolizumab pegol 400 mg), 24 (Control)					
Heterogeneity: Chi^2 = 3.29, df = 3 (P = 0.35); I^2 =9%					
Test for overall effect: Z = 2.97 (P = 0.0029)					
Test for subgroup differences: Not applicable					



Analysis 9.42. Comparison 9 Safety, certolizumab 400 mg, Outcome 42 Gastrointestinal disorders.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 42 Gastrointestinal disorders

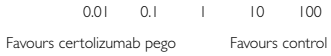
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CDP870-014 2009	22/124	19/119		97.4 %	1.13 [0.58, 2.22]
RAPID1 2005	0/389	1/199		2.6 %	0.05 [0.00, 3.28]
Total (95% CI)	**513**	**318**		**100.0 %**	**1.05 [0.54, 2.03]**

Total events: 22 (Certolizumab pegol 400 mg), 20 (Control)

Heterogeneity: $Chi^2 = 2.07$, df = 1 (P = 0.15); $I^2 = 52\%$

Test for overall effect: Z = 0.14 (P = 0.89)

Test for subgroup differences: Not applicable



Analysis 9.43. Comparison 9 Safety, certolizumab 400 mg, Outcome 43 Hematologic abnormalities.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 43 Hematologic abnormalities

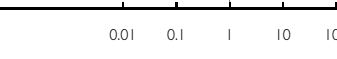
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
NCT00791999 JRAPID (1)	1/85	0/77		18.3 %	6.73 [0.13, 340.56]
RAPID1 2005	3/389	2/199		81.7 %	0.76 [0.12, 4.86]
Total (95% CI)	**474**	**276**		**100.0 %**	**1.13 [0.21, 6.07]**

Total events: 4 (Certolizumab pegol 400 mg), 2 (Control)

Heterogeneity: $Chi^2 = 0.97$, df = 1 (P = 0.32); $I^2 = 0.0\%$

Test for overall effect: Z = 0.14 (P = 0.89)

Test for subgroup differences: Not applicable



(1) 1 patinet with bone marrow failure

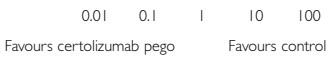
Analysis 9.44. Comparison 9 Safety, certolizumab 400 mg, Outcome 44 Decreased Haemoglobin.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 44 Decreased Haemoglobin

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID1 2005	1/389	1/199		100.0 %	0.49 [0.03, 9.10]
Total (95% CI)	**389**	**199**		**100.0 %**	**0.49 [0.03, 9.10]**
Total events: 1 (Certolizumab pegol 400 mg), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.48 (P = 0.63)					
Test for subgroup differences: Not applicable					

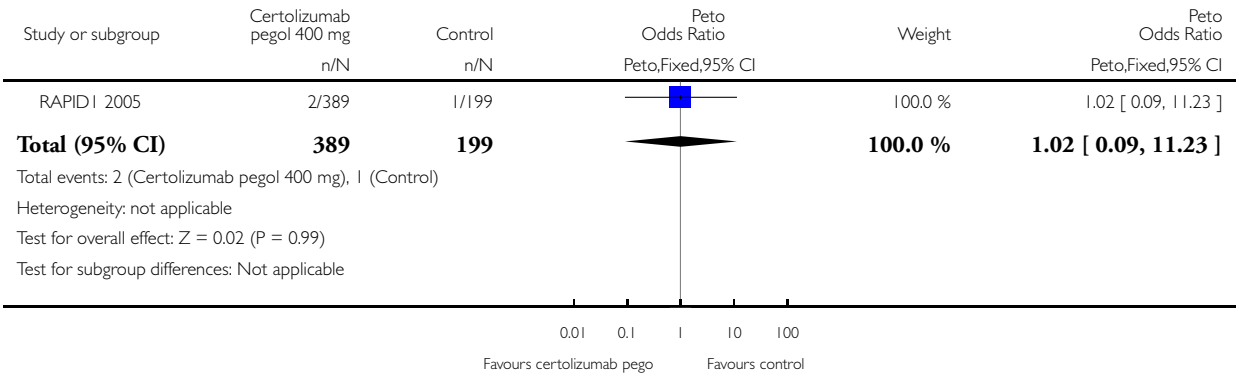


Analysis 9.45. Comparison 9 Safety, certolizumab 400 mg, Outcome 45 Increased platelet count.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 45 Increased platelet count

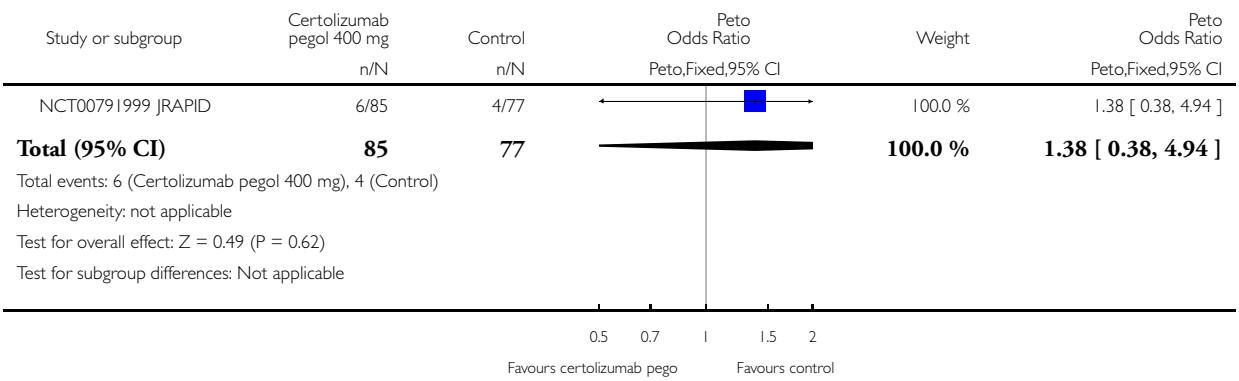


Analysis 9.46. Comparison 9 Safety, certolizumab 400 mg, Outcome 46 Skin and subcutaneous tissue disorders.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 46 Skin and subcutaneous tissue disorders

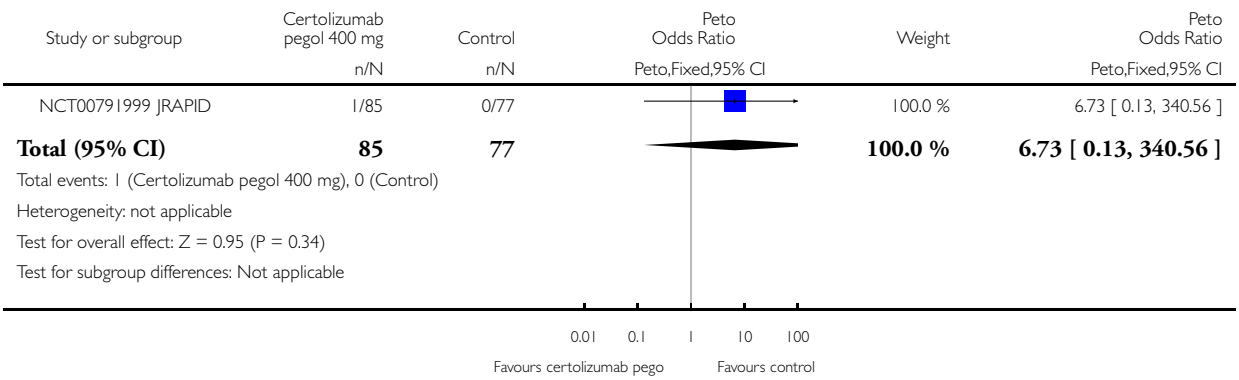


Analysis 9.47. Comparison 9 Safety, certolizumab 400 mg, Outcome 47 Acute miocardial infarction.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 47 Acute miocardial infarction

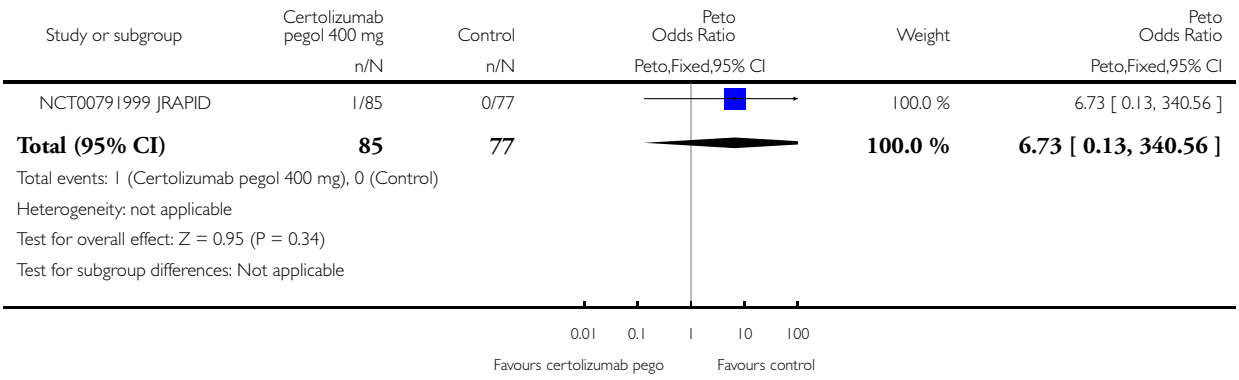


Analysis 9.48. Comparison 9 Safety, certolizumab 400 mg, Outcome 48 Corneal Perforation.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 48 Corneal Perforation

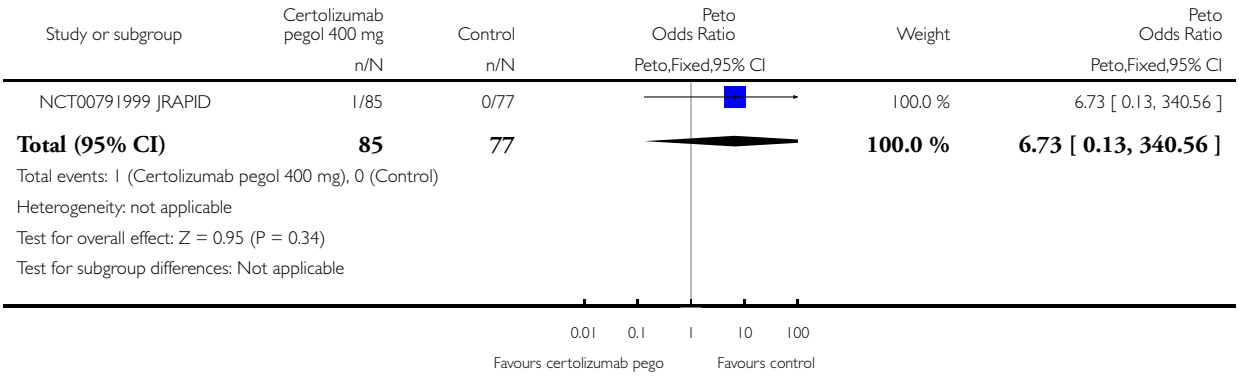


Analysis 9.49. Comparison 9 Safety, certolizumab 400 mg, Outcome 49 Conjunctivitis allergic.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 49 Conjunctivitis allergic

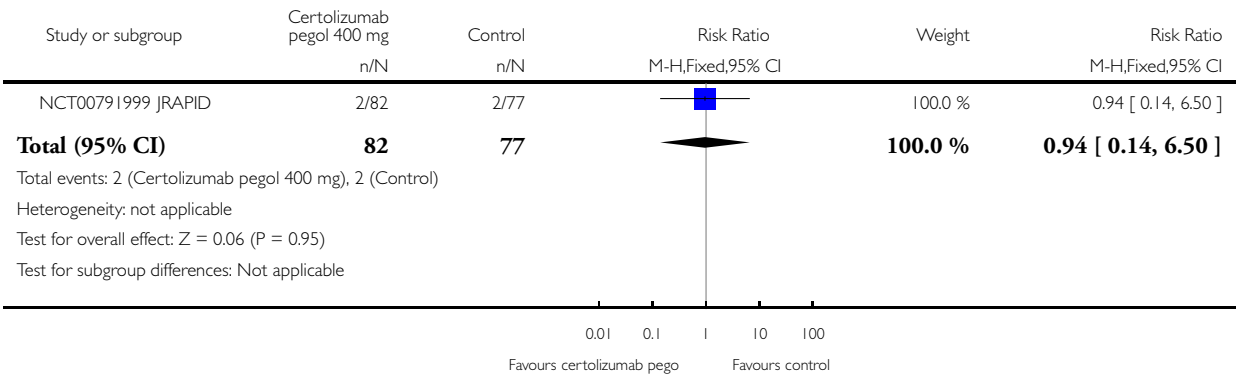


Analysis 9.50. Comparison 9 Safety, certolizumab 400 mg, Outcome 50 Periodontitis.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 50 Periodontitis

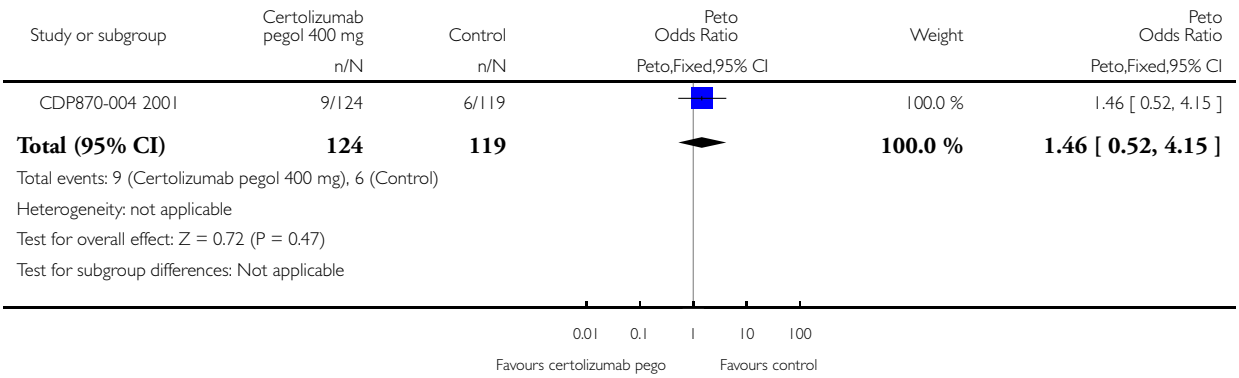


Analysis 9.51. Comparison 9 Safety, certolizumab 400 mg, Outcome 51 Fatigue.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety, certolizumab 400 mg

Outcome: 51 Fatigue

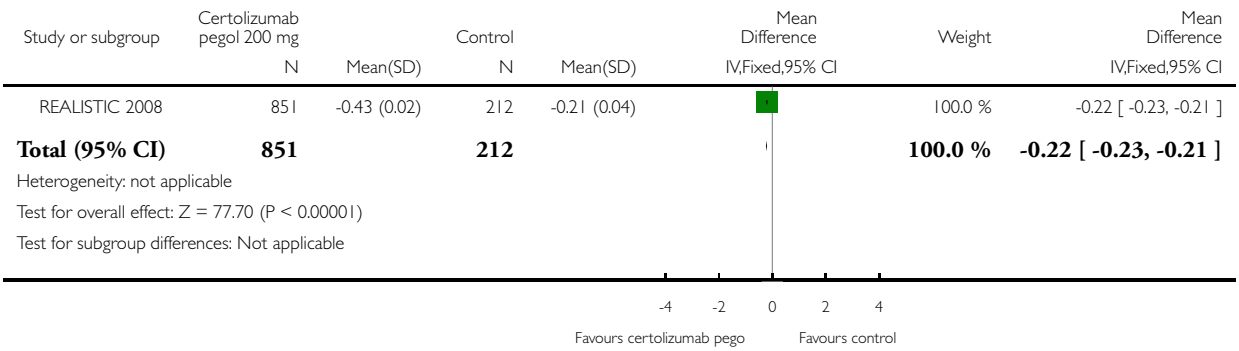


Analysis 10.1. Comparison 10 Mean HAQ-DI from baseline at week 12, Outcome 1 certolizumab pegol 200 mg sc.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 10 Mean HAQ-DI from baseline at week 12

Outcome: 1 certolizumab pegol 200 mg sc



Analysis 11.1. Comparison 11 Mean HAQ-DI from baseline at week 24, Outcome 1 certolizumab pegol 200 mg sc.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 11 Mean HAQ-DI from baseline at week 24

Outcome: 1 certolizumab pegol 200 mg sc

Study or subgroup	Certolizumab pegol 200 mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
RAPID1 2005	393	-0.58 (0.59)	199	-0.17 (0.56)		33.9 %	-0.41 [-0.51, -0.31]
NCT00993317	81	-0.54 (0.51)	40	-0.17 (0.7)		9.6 %	-0.37 [-0.61, -0.13]
RAPID2 2007	246	-0.5 (0.47)	127	-0.14 (0.45)		33.7 %	-0.36 [-0.46, -0.26]
CERTAIN 2008	91	-0.25 (0.46)	91	-0.03 (0.49)		22.8 %	-0.22 [-0.36, -0.08]
Total (95% CI)	**811**		**457**			**100.0 %**	**-0.35 [-0.43, -0.26]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.92$, df = 3 (P = 0.18); $I^2 = 39\%$

Test for overall effect: Z = 8.32 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 11.2. Comparison 11 Mean HAQ-DI from baseline at week 24, Outcome 2 certolizumab 400 mg sc.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 11 Mean HAQ-DI from baseline at week 24

Outcome: 2 certolizumab 400 mg sc

Study or subgroup	Certolizumab 400 mg sc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
CDP870-014 2009 (1)	124	-0.32 (0.7)	119	-0.09 (0.15)		23.2 %	-0.23 [-0.36, -0.10]
FAST4WARD 2005 (2)	111	-0.36 (0.51)	109	0.13 (0.51)		22.0 %	-0.49 [-0.62, -0.36]
RAPID1 2005	390	-0.6 (0.59)	199	-0.17 (0.56)		27.4 %	-0.43 [-0.53, -0.33]
RAPID2 2007	246	-0.5 (0.47)	127	-0.14 (0.45)		27.4 %	-0.36 [-0.46, -0.26]
Total (95% CI)	**871**		**554**			**100.0 %**	**-0.38 [-0.48, -0.28]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 9.17$, df = 3 (P = 0.03); $I^2 = 67\%$

Test for overall effect: Z = 7.53 (P < 0.00001)

Test for subgroup differences: Not applicable

(1) In CDP870-014 we have obtained standard deviations from p values according to the Handbook section 7.7.3.7. calculating t values , EE and finally SD

(2) In FAST4WARD we have obtained standard deviations from p values according to the Handbook section 7.7.3.7

Analysis 12.1. Comparison 12 HAQ-DI at 24 weeks, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 12 HAQ-DI at 24 weeks, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 certolizumab pegol 200 mg sc							
CERTAIN 2008	91	-0.25 (0.46)	91	-0.03 (0.49)		13.3 %	-0.22 [-0.36, -0.08]
RAPID1 2005	393	-0.58 (0.59)	100	-0.17 (0.56)		14.7 %	-0.41 [-0.53, -0.29]
RAPID2 2007	246	-0.5 (0.47)	64	-0.14 (0.45)		14.6 %	-0.36 [-0.48, -0.24]
Subtotal (95% CI)	**730**		**255**			**42.7 %**	**-0.33 [-0.44, -0.23]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.21$, df = 2 (P = 0.12); $I^2 = 53\%$							
Test for overall effect: Z = 6.05 (P < 0.00001)							
2 certolizumab pegol 400 mg sc							
CDP870-014 2009 (1)	124	-0.32 (0.7)	119	-0.09 (0.15)		14.5 %	-0.23 [-0.36, -0.10]
FAST4WARD 2005	111	-0.36 (0.51)	109	0.13 (0.51)		13.7 %	-0.49 [-0.62, -0.36]
RAPID1 2005	390	-0.6 (0.59)	99	-0.17 (0.56)		14.6 %	-0.43 [-0.55, -0.31]
RAPID2 2007	246	-0.5 (0.47)	63	-0.14 (0.45)		14.5 %	-0.36 [-0.49, -0.23]
Subtotal (95% CI)	**871**		**390**			**57.3 %**	**-0.38 [-0.48, -0.27]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 8.67$, df = 3 (P = 0.03); $I^2 = 65\%$							
Test for overall effect: Z = 6.79 (P < 0.00001)							
Total (95% CI)	**1601**		**645**			**100.0 %**	**-0.36 [-0.43, -0.29]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 13.43$, df = 6 (P = 0.04); $I^2 = 55\%$							
Test for overall effect: Z = 9.67 (P < 0.00001)							
Test for subgroup differences: $Chi^2 = 0.30$, df = 1 (P = 0.59), $I^2 = 0.0\%$							

(1) In CDP870-014 we have obtained standard deviations from p values according to the Handbook section 7.7.3.7. calculating t values , EE and finally SD

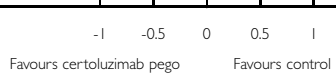
Analysis 13.1. Comparison 13 HAQ-DI at 52 weeks, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 13 HAQ-DI at 52 weeks, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 certolizumab pegol 200 mg sc							
RAPID1 2005	393	-0.6 (0.59)	100	-0.18 (0.56)		50.2 %	-0.42 [-0.54, -0.30]
Subtotal (95% CI)	**393**		**100**			**50.2 %**	**-0.42 [-0.54, -0.30]**
Heterogeneity: not applicable							
Test for overall effect: Z = 6.62 (P < 0.00001)							
2 certolizumab pegol 400 mg sc							
RAPID1 2005	390	-0.63 (0.59)	99	-0.18 (0.56)		49.8 %	-0.45 [-0.57, -0.33]
Subtotal (95% CI)	**390**		**99**			**49.8 %**	**-0.45 [-0.57, -0.33]**
Heterogeneity: not applicable							
Test for overall effect: Z = 7.06 (P < 0.00001)							
Total (95% CI)	**783**		**199**			**100.0 %**	**-0.43 [-0.52, -0.35]**
Heterogeneity: Chi^2 = 0.11, df = 1 (P = 0.74); I^2 =0.0%							
Test for overall effect: Z = 9.68 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.11, df = 1 (P = 0.74), I^2 =0.0%							



Analysis 14.1. Comparison 14 SF-36 Physical Component Summary (PCS), week 24, Outcome 1 certolizumab pegol 200 mg sc.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 14 SF-36 Physical Component Summary (PCS), week 24

Outcome: 1 certolizumab pegol 200 mg sc

Study or subgroup	Certolizumab pegol 200 mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
CERTAIN 2008	82	6 (7.5)	82	1.7 (7.56)		20.9 %	4.30 [2.00, 6.60]
RAPID1 2005	393	7.7 (7.93)	199	1.8 (8.46)		45.6 %	5.90 [4.49, 7.31]
RAPID2 2007	246	5.23 (8.31)	127	0.93 (8)		33.5 %	4.30 [2.56, 6.04]
Total (95% CI)	**721**		**408**			**100.0 %**	**5.03 [3.90, 6.16]**

Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 2.51$, df = 2 (P = 0.29); $I^2 = 20\%$

Test for overall effect: Z = 8.72 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 14.2. Comparison 14 SF-36 Physical Component Summary (PCS), week 24, Outcome 2 certolizumab pegol 400 mg sc.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 14 SF-36 Physical Component Summary (PCS), week 24

Outcome: 2 certolizumab pegol 400 mg sc

Study or subgroup	Certolizumab pegol 400 mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
CDP870-014 2009 (1)	124	8.44 (19.76)	119	3.44 (8.07)		12.4 %	5.00 [1.23, 8.77]
RAPID1 2005	390	8.3 (7.9)	199	1.8 (8.46)		48.5 %	6.50 [5.09, 7.91]
RAPID2 2007	246	5.46 (8.31)	127	0.93 (8)		39.1 %	4.53 [2.79, 6.27]
Total (95% CI)	**760**		**445**			**100.0 %**	**5.54 [4.11, 6.97]**

Heterogeneity: $Tau^2 = 0.58$; $Chi^2 = 3.10$, df = 2 (P = 0.21); $I^2 = 36\%$

Test for overall effect: Z = 7.60 (P < 0.00001)

Test for subgroup differences: Not applicable

(1) Calculating SD according to Handbook from p values

Analysis 15.1. Comparison 15 SF-36 Mental Component Summary (MCS), week 24, Outcome 1 certolizumab pegol 200 mg sc.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 15 SF-36 Mental Component Summary (MCS), week 24

Outcome: 1 certolizumab pegol 200 mg sc

Study or subgroup	Certolizumab pegol 200 mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
RAPID1 2005	393	6.3 (11.89)	199	2.3 (11.29)		56.9 %	4.00 [2.04, 5.96]
RAPID2 2007	246	6.05 (10.82)	127	1.63 (10.36)		43.1 %	4.42 [2.17, 6.67]
Total (95% CI)	**639**		**326**			**100.0 %**	**4.18 [2.70, 5.66]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.08$, df = 1 (P = 0.78); $I^2 = 0.0\%$

Test for overall effect: Z = 5.54 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 15.2. Comparison 15 SF-36 Mental Component Summary (MCS), week 24, Outcome 2 certolizumab pegol 400 mg sc.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 15 SF-36 Mental Component Summary (MCS), week 24

Outcome: 2 certolizumab pegol 400 mg sc

Study or subgroup	Certolizumab pegol 400 mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
CDP870-014 2009 (1)	124	4.6 (13.87)	119	1.58 (4.76)		24.7 %	3.02 [0.43, 5.61]
RAPID1 2005	390	6.5 (11.85)	199	2.3 (11.29)		43.0 %	4.20 [2.24, 6.16]
RAPID2 2007	246	6.28 (10.98)	127	1.63 (10.36)		32.2 %	4.65 [2.39, 6.91]
Total (95% CI)	**760**		**445**			**100.0 %**	**4.05 [2.77, 5.34]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.90$, df = 2 (P = 0.64); $I^2 = 0.0\%$

Test for overall effect: Z = 6.18 (P < 0.00001)

Test for subgroup differences: Not applicable

(1) Calculating SD according to Handbook from p values

Analysis 16.1. Comparison 16 SF-36 Physical Component Summary (PCS), week 52, Outcome 1 certolizumab 200 mg sc.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 16 SF-36 Physical Component Summary (PCS), week 52

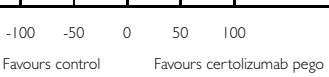
Outcome: 1 certolizumab 200 mg sc

Study or subgroup	Certolizumab pegol 200 mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	393	7.79 (8.72)	199	1.73 (8.61)		100.0 %	6.06 [4.59, 7.53]
Total (95% CI)	**393**		**199**			**100.0 %**	**6.06 [4.59, 7.53]**

Heterogeneity: not applicable

Test for overall effect: Z = 8.05 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 16.2. Comparison 16 SF-36 Physical Component Summary (PCS), week 52, Outcome 2 certolizumab 400 mg sc.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 16 SF-36 Physical Component Summary (PCS), week 52

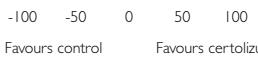
Outcome: 2 certolizumab 400 mg sc

Study or subgroup	Certolizumab pegol 400 mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	390	8.61 (8.49)	199	1.73 (8.61)		100.0 %	6.88 [5.42, 8.34]
Total (95% CI)	**390**		**199**			**100.0 %**	**6.88 [5.42, 8.34]**

Heterogeneity: not applicable

Test for overall effect: Z = 9.22 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 17.1. Comparison 17 SF-36 Mental Component Summary (MCS), week 52, Outcome 1 certolizumab pegol 200 mg sc.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 17 SF-36 Mental Component Summary (MCS), week 52

Outcome: 1 certolizumab pegol 200 mg sc

Study or subgroup	Certolizumab 200 mg sc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	393	6.35 (11.1)	199	2.05 (11.14)		100.0 %	4.30 [2.40, 6.20]
Total (95% CI)	**393**		**199**			**100.0 %**	**4.30 [2.40, 6.20]**

Heterogeneity: not applicable

Test for overall effect: Z = 4.44 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 17.2. Comparison 17 SF-36 Mental Component Summary (MCS), week 52, Outcome 2 certolizumab pegol 400 mg sc.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 17 SF-36 Mental Component Summary (MCS), week 52

Outcome: 2 certolizumab pegol 400 mg sc

Study or subgroup	Certolizumab pegol 400 mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	390	6.35 (11.06)	199	2.05 (11.14)		100.0 %	4.30 [2.40, 6.20]
Total (95% CI)	**390**		**199**			**100.0 %**	**4.30 [2.40, 6.20]**

Heterogeneity: not applicable

Test for overall effect: Z = 4.44 (P < 0.00001)

Test for subgroup differences: Not applicable

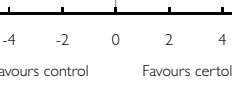
Analysis 18.1. Comparison 18 SF-36 Physical Component Summary (PCS) at week 24, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 18 SF-36 Physical Component Summary (PCS) at week 24, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 certolizumab pegol 200 mg sc							
CERTAIN 2008	82	6 (7.5)	82	1.7 (7.56)		15.9 %	4.30 [2.00, 6.60]
RAPID1 2005	393	7.7 (7.93)	100	1.8 (8.46)		25.1 %	5.90 [4.07, 7.73]
RAPID2 2007	246	5.23 (8.31)	64	0.93 (8)		17.2 %	4.30 [2.08, 6.52]
Subtotal (95% CI)	**721**		**246**			**58.2 %**	**4.99 [3.79, 6.20]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.66$, df = 2 (P = 0.44); $I^2 = 0.0\%$							
Test for overall effect: Z = 8.12 (P < 0.00001)							
2 certolizumab pegol 400 mg sc							
RAPID1 2005	390	8.3 (7.9)	99	1.8 (8.46)		24.9 %	6.50 [4.66, 8.34]
RAPID2 2007	246	5.46 (8.31)	63	0.93 (8)		17.0 %	4.53 [2.30, 6.76]
Subtotal (95% CI)	**636**		**162**			**41.8 %**	**5.62 [3.70, 7.54]**
Heterogeneity: $Tau^2 = 0.85$; $Chi^2 = 1.78$, df = 1 (P = 0.18); $I^2 = 44\%$							
Test for overall effect: Z = 5.74 (P < 0.00001)							
Total (95% CI)	**1357**		**408**			**100.0 %**	**5.29 [4.37, 6.21]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.00$, df = 4 (P = 0.41); $I^2 = 0\%$							
Test for overall effect: Z = 11.28 (P < 0.00001)							
Test for subgroup differences: $Chi^2 = 0.30$, df = 1 (P = 0.59), $I^2 = 0.0\%$							



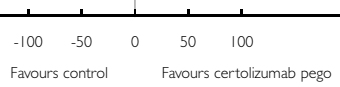
Analysis 19.1. Comparison 19 SF-36 Mental Component Summary (MCS) at week 24, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 19 SF-36 Mental Component Summary (MCS) at week 24, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 certolizumab pegol 200 mg sc							
CERTAIN 2008	83	5.2 (8.43)	85	1.2 (7.72)		19.1 %	4.00 [1.55, 6.45]
RAPID1 2005	393	6.3 (11.89)	100	2.3 (11.29)		18.2 %	4.00 [1.49, 6.51]
RAPID2 2007	246	6.05 (10.82)	64	1.63 (10.36)		13.8 %	4.42 [1.54, 7.30]
Subtotal (95% CI)	**722**		**249**			**51.2 %**	**4.11 [2.62, 5.61]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.06$, df = 2 (P = 0.97); $I^2 = 0.0\%$							
Test for overall effect: Z = 5.39 (P < 0.00001)							
2 certolizumab pegol 400 mg sc							
CDP870-014 2009 (1)	124	4.6 (13.87)	119	1.58 (4.76)		17.1 %	3.02 [0.43, 5.61]
RAPID1 2005	390	6.5 (11.85)	99	2.3 (11.29)		18.1 %	4.20 [1.68, 6.72]
RAPID2 2007	246	6.28 (10.98)	63	1.63 (10.36)		13.6 %	4.65 [1.75, 7.55]
Subtotal (95% CI)	**760**		**281**			**48.8 %**	**3.91 [2.38, 5.44]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.76$, df = 2 (P = 0.69); $I^2 = 0.0\%$							
Test for overall effect: Z = 5.00 (P < 0.00001)							
Total (95% CI)	**1482**		**530**			**100.0 %**	**4.01 [2.94, 5.08]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.85$, df = 5 (P = 0.97); $I^2 = 0.0\%$							
Test for overall effect: Z = 7.35 (P < 0.00001)							
Test for subgroup differences: $Chi^2 = 0.03$, df = 1 (P = 0.85), $I^2 = 0.0\%$							



(1) Calculating SD according to Handbook from p values

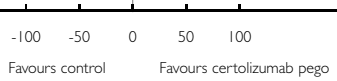
Analysis 20.1. Comparison 20 SF-36 Physical Component Summary (PCS) at week 52, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 20 SF-36 Physical Component Summary (PCS) at week 52, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 certolizumab pegol 200 mg sc							
RAPID1 2005	393	7.79 (8.72)	100	1.73 (8.61)		50.0 %	6.06 [4.17, 7.95]
Subtotal (95% CI)	**393**		**100**			**50.0 %**	**6.06 [4.17, 7.95]**
Heterogeneity: not applicable							
Test for overall effect: Z = 6.27 (P < 0.00001)							
2 certolizumab pegol 400 mg sc							
RAPID1 2005	390	8.61 (8.49)	99	1.73 (8.61)		50.0 %	6.88 [4.99, 8.77]
Subtotal (95% CI)	**390**		**99**			**50.0 %**	**6.88 [4.99, 8.77]**
Heterogeneity: not applicable							
Test for overall effect: Z = 7.12 (P < 0.00001)							
Total (95% CI)	**783**		**199**			**100.0 %**	**6.47 [5.13, 7.81]**
Heterogeneity: Chi^2 = 0.36, df = 1 (P = 0.55); I^2 =0.0%							
Test for overall effect: Z = 9.47 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.36, df = 1 (P = 0.55), I^2 =0.0%							



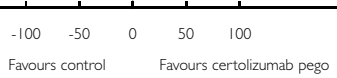
Analysis 21.1. Comparison 21 SF-36 Mental Component Summary (MCS) at week 52, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 21 SF-36 Mental Component Summary (MCS) at week 52, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 certolizumab pegol 200 mg sc							
RAPID1 2005	393	6.35 (11.1)	100	2.05 (11.14)		50.2 %	4.30 [1.86, 6.74]
Subtotal (95% CI)	**393**		**100**			**50.2 %**	**4.30 [1.86, 6.74]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.45 (P = 0.00056)							
2 certolizumab pegol 400 mg sc							
RAPID1 2005	390	6.35 (11.06)	99	2.05 (11.14)		49.8 %	4.30 [1.85, 6.75]
Subtotal (95% CI)	**390**		**99**			**49.8 %**	**4.30 [1.85, 6.75]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.43 (P = 0.00059)							
Total (95% CI)	**783**		**199**			**100.0 %**	**4.30 [2.57, 6.03]**
Heterogeneity: Chi^2 = 0.0, df = 1 (P = 1.00); I^2 =0.0%							
Test for overall effect: Z = 4.87 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.0, df = 1 (P = 1.00), I^2 =0.0%							



Analysis 22.1. Comparison 22 Disease Activity Score (DAS-28) (ESR) remission (< 2.6) at 12 weeks, Outcome 1 Proportion of patients achieving remission 12 weeks certolizumab 200 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 22 Disease Activity Score (DAS-28) (ESR) remission (< 2.6) at 12 weeks

Outcome: 1 Proportion of patients achieving remission 12 weeks certolizumab 200 mg

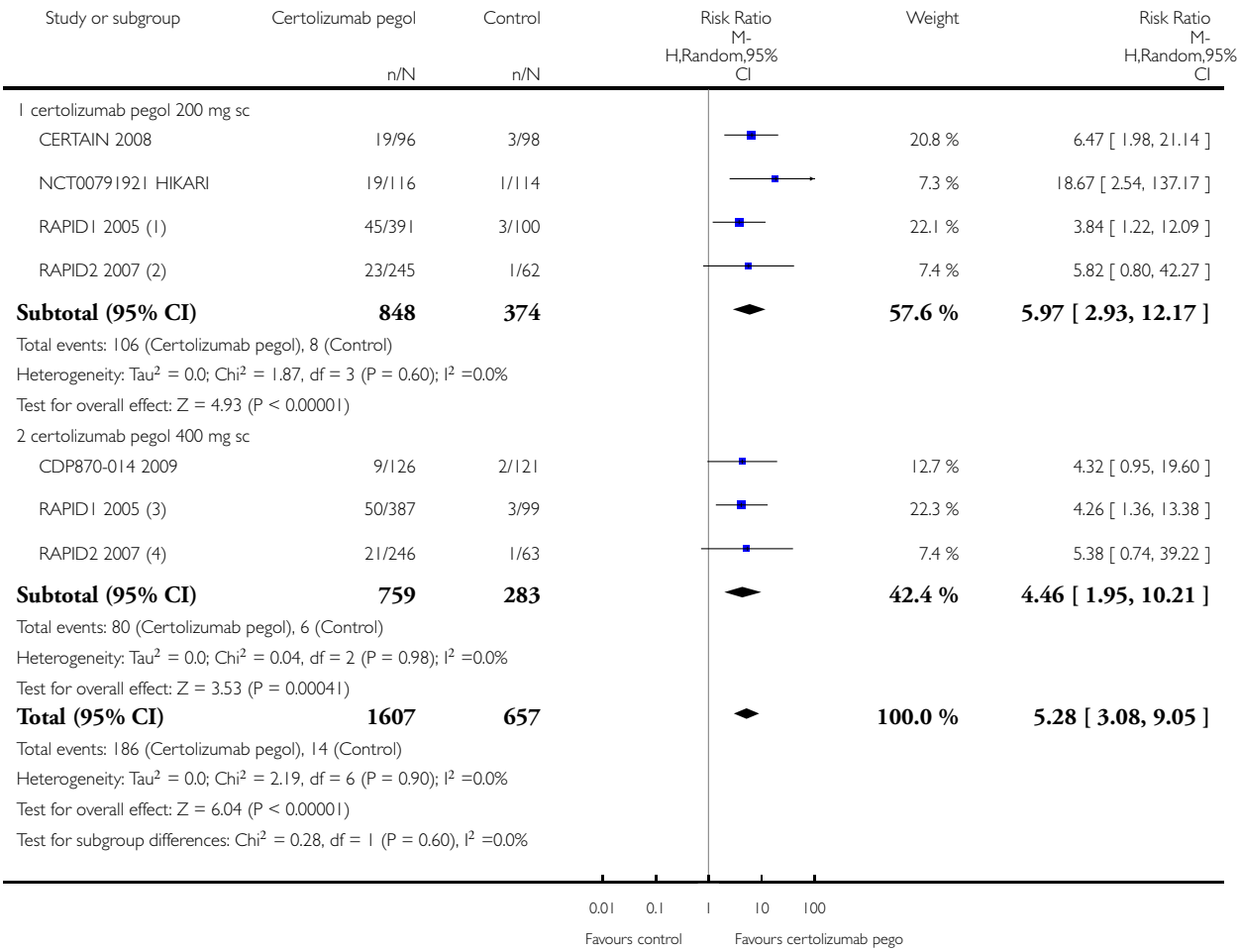
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
REALISTIC 2008	136/851	12/212		100.0 %	2.36 [1.53, 3.65]
Total (95% CI)	**851**	**212**		**100.0 %**	**2.36 [1.53, 3.65]**
Total events: 136 (Certolizumab pegol 200 mg), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.88 (P = 0.00010)					
Test for subgroup differences: Not applicable					

Analysis 23.1. Comparison 23 Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any dose, 24 weeks, Outcome 1 Proportion of patients achieving remission 24 weeks.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 23 Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any dose, 24 weeks

Outcome: 1 Proportion of patients achieving remission 24 weeks



(1) UCB report for NICE quoted Certolizumab n=391 and placebo n=196

(2) In NICE report UCB quoted certoluzimab n= 245 and placebo n =125

(3) In NICE report UCB quoted Certolizumab n= 387 and placebo n = 196

(4) In NICE report UCB quoted placebo n =125

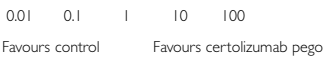
Analysis 24.1. Comparison 24 Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any dose, 52 weeks, Outcome 1 Proportion of patients achieving remission 52 weeks.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 24 Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any dose, 52 weeks

Outcome: 1 Proportion of patients achieving remission 52 weeks

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 certolizumab pegol 200 mg sc					
RAPID1 2005 (1)	62/391	3/100		50.0 %	5.29 [1.69, 16.49]
Subtotal (95% CI)	**391**	**100**		**50.0 %**	**5.29 [1.69, 16.49]**
Total events: 62 (Certolizumab pegol), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.87 (P = 0.0041)					
2 certolizumab pegol 400 mg sc					
RAPID1 2005 (2)	74/387	3/99		50.0 %	6.31 [2.03, 19.59]
Subtotal (95% CI)	**387**	**99**		**50.0 %**	**6.31 [2.03, 19.59]**
Total events: 74 (Certolizumab pegol), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.19 (P = 0.0014)					
Total (95% CI)	**778**	**199**		**100.0 %**	**5.80 [2.60, 12.94]**
Total events: 136 (Certolizumab pegol), 6 (Control)					
Heterogeneity: Chi^2 = 0.05, df = 1 (P = 0.83); I^2 =0.0%					
Test for overall effect: Z = 4.29 (P = 0.000018)					
Test for subgroup differences: Chi^2 = 0.05, df = 1 (P = 0.83), I^2 =0.0%					



(1) In NICE report UCB quoted placebo certoluzimab n= 391 and placebo n =196

(2) UCB report for NICE quoted Certolizumab n=387

Analysis 25.1. Comparison 25 Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any time, Outcome 1 Proportion of patients achieving remission 12 weeks certolizumab 200 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 25 Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any time

Outcome: 1 Proportion of patients achieving remission 12 weeks certolizumab 200 mg

Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
REALISTIC 2008	136/851	12/212		100.0 %	2.82 [1.60, 5.00]
Total (95% CI)	**851**	**212**		**100.0 %**	**2.82 [1.60, 5.00]**
Total events: 136 (Certolizumab pegol 200 mg), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.56 (P = 0.00036)					
Test for subgroup differences: Not applicable					

Analysis 25.2. Comparison 25 Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any time, Outcome 2 Proportion of patients achieving remission 24 weeks certolizumab 200 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 25 Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any time

Outcome: 2 Proportion of patients achieving remission 24 weeks certolizumab 200 mg

Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
CERTAIN 2008	19/96	3/98		36.3 %	6.47 [1.98, 21.14]
RAPID1 2005 (1)	45/391	3/196		38.1 %	7.52 [2.37, 23.89]
RAPID2 2007 (2)	23/245	1/125		12.8 %	11.73 [1.60, 85.89]
NCT00791921 HIKARI	19/116	1/114		12.8 %	18.67 [2.54, 137.17]
Total (95% CI)	**848**	**533**		**100.0 %**	**8.47 [4.15, 17.28]**

Total events: 106 (Certolizumab pegol 200 mg), 8 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.97$, df = 3 ($P = 0.81$); $I^2 = 0.0\%$

Test for overall effect: $Z = 5.87$ ($P < 0.00001$)

Test for subgroup differences: Not applicable

(1) UCB report for NICE quote Certolizumab n=391

(2) UCB report for NICE quote Certolizumab n=245

Analysis 25.3. Comparison 25 Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any time, Outcome 3 Proportion of patients achieving remission 24 weeks certolizumab 400 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 25 Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any time

Outcome: 3 Proportion of patients achieving remission 24 weeks certolizumab 400 mg

Study or subgroup	Certolizumab 400 mg n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
CDP870-014 2009	9/126	2/121		30.3 %	4.32 [0.95, 19.60]
RAPID1 2005 (1)	50/387	3/196		52.2 %	8.44 [2.67, 26.72]
RAPID2 2007	21/246	1/125		17.4 %	10.67 [1.45, 78.41]
Total (95% CI)	**759**	**442**		**100.0 %**	**7.18 [3.12, 16.50]**

Total events: 80 (Certolizumab 400 mg), 6 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.69$, df = 2 (P = 0.71); $I^2 = 0.0\%$

Test for overall effect: Z = 4.64 (P < 0.00001)

Test for subgroup differences: Not applicable

(1) UCB report for NICE quote Certolizumab n=387

Analysis 25.4. Comparison 25 Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any time, Outcome 4 Proportion of patients achieving remission 52 weeks certolizumab 200 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 25 Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any time

Outcome: 4 Proportion of patients achieving remission 52 weeks certolizumab 200 mg

Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RAPID1 2005 (1)	62/391	3/196		100.0 %	10.36 [3.29, 32.58]
Total (95% CI)	**391**	**196**		**100.0 %**	**10.36 [3.29, 32.58]**
Total events: 62 (Certolizumab pegol 200 mg), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.00 (P = 0.000064)					
Test for subgroup differences: Not applicable					

(1) UCB report for NICE quote Certolizumab n=391

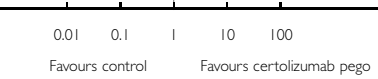
Analysis 25.5. Comparison 25 Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any time, Outcome 5 Proportion of patients achieving remission 52 weeks certolizumab 400 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 25 Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any time

Outcome: 5 Proportion of patients achieving remission 52 weeks certolizumab 400 mg

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RAPID1 2005 (1)	74/387	3/196		100.0 %	12.49 [3.99, 39.12]
Total (95% CI)	**387**	**196**		**100.0 %**	**12.49 [3.99, 39.12]**
Total events: 74 (Certolizumab pegol 400 mg), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.34 (P = 0.000015)					
Test for subgroup differences: Not applicable					



(1) UCB report for NICE quote Certolizumab n=387

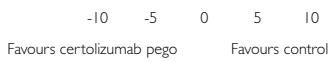
Analysis 26.1. Comparison 26 DAS-28 at 12 weeks, 200 mg certolizumab, Outcome 1 DAS 28 (ESR) change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 26 DAS-28 at 12 weeks, 200 mg certolizumab

Outcome: 1 DAS 28 (ESR) change from baseline

Study or subgroup	Certolizumab 200 mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
REALISTIC 2008	851	-1.64 (0)	212	-0.78 (0)			Not estimable
Total (95% CI)	**851**		**212**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Test for subgroup differences: Not applicable							



Analysis 27.1. Comparison 27 DAS-28 at 24 weeks, 400 mg certolizumab, Outcome 1 DAS 28 (ESR) change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 27 DAS-28 at 24 weeks, 400 mg certolizumab

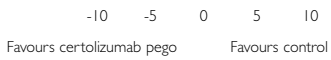
Outcome: 1 DAS 28 (ESR) change from baseline

Study or subgroup	Certolizumab pegol 400 mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
FAST4WARD 2005	111	-1.5 (2)	109	-0.6 (2)		47.5 %	-0.90 [-1.43, -0.37]
RAPID2 2007	246	-2.46 (1.31)	127	-0.5 (1.05)		52.5 %	-1.96 [-2.21, -1.71]
Total (95% CI)	**357**		**236**			**100.0 %**	**-1.46 [-2.49, -0.42]**

Heterogeneity: $Tau^2 = 0.52$; $Chi^2 = 12.71$, df = 1 (P = 0.00036); $I^2 = 92\%$

Test for overall effect: Z = 2.75 (P = 0.0059)

Test for subgroup differences: Not applicable



Analysis 28.1. Comparison 28 DAS-28 at week 52, certolizumab 200 mg, Outcome 1 DAS 28 (ESR) Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 28 DAS-28 at week 52, certolizumab 200 mg

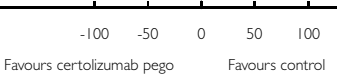
Outcome: 1 DAS 28 (ESR) Change from baseline

Study or subgroup	Certolizumab pegol 200 mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	393	-3.3 (1.3)	199	-2.4 (1.3)		100.0 %	-0.90 [-1.12, -0.68]
Total (95% CI)	**393**		**199**			**100.0 %**	**-0.90 [-1.12, -0.68]**

Heterogeneity: not applicable

Test for overall effect: Z = 7.96 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 29.1. Comparison 29 DAS-28 at week 52, certolizumab 400 mg, Outcome 1 DAS 28 (ESR) Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 29 DAS-28 at week 52, certolizumab 400 mg

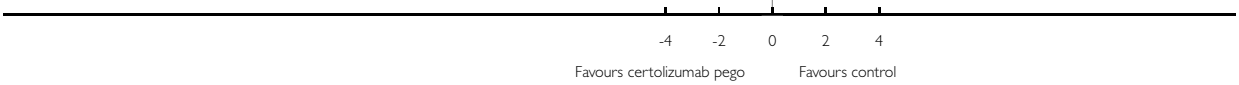
Outcome: 1 DAS 28 (ESR) Change from baseline

Study or subgroup	Certolizumab pegol 400 mg		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
RAPID1 2005	390	-3.4 (1.4)	199	-2.4 (1.3)		100.0 %	-1.00 [-1.23, -0.77]
Total (95% CI)	**390**		**199**			**100.0 %**	**-1.00 [-1.23, -0.77]**

Heterogeneity: not applicable

Test for overall effect: Z = 8.60 (P < 0.00001)

Test for subgroup differences: Not applicable



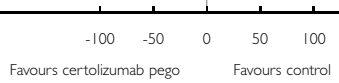
Analysis 30.1. Comparison 30 DAS-28 at 24 weeks, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 30 DAS-28 at 24 weeks, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 certolizumab pegol 200 mg sc							
RAPID2 2007	246	-2.27 (1.38)	64	-0.5 (1.05)		35.7 %	-1.77 [-2.08, -1.46]
Subtotal (95% CI)	**246**		**64**			**35.7 %**	**-1.77 [-2.08, -1.46]**
Heterogeneity: not applicable							
Test for overall effect: Z = 11.20 (P < 0.00001)							
2 certolizumab pegol 400 mg sc							
FAST4WARD 2005	111	-1.5 (2)	109	-0.6 (2)		28.6 %	-0.90 [-1.43, -0.37]
RAPID2 2007	246	-2.46 (1.31)	63	-0.5 (1.05)		35.8 %	-1.96 [-2.27, -1.65]
Subtotal (95% CI)	**357**		**172**			**64.3 %**	**-1.45 [-2.49, -0.41]**
Heterogeneity: Tau^2 = 0.51; Chi^2 = 11.56, df = 1 (P = 0.00067); I^2 =91%							
Test for overall effect: Z = 2.74 (P = 0.0061)							
Total (95% CI)	**603**		**236**			**100.0 %**	**-1.59 [-2.10, -1.08]**
Heterogeneity: Tau^2 = 0.17; Chi^2 = 11.70, df = 2 (P = 0.003); I^2 =83%							
Test for overall effect: Z = 6.07 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.33, df = 1 (P = 0.57), I^2 =0.0%							



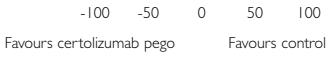
Analysis 31.1. Comparison 31 DAS-28 at 52 weeks, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 31 DAS-28 at 52 weeks, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 certolizumab pegol 200 mg sc							
RAPID1 2005	393	-3.3 (1.3)	100	-2.4 (1.3)		51.0 %	-0.90 [-1.19, -0.61]
Subtotal (95% CI)	**393**		**100**			**51.0 %**	**-0.90 [-1.19, -0.61]**
Heterogeneity: not applicable							
Test for overall effect: Z = 6.18 (P < 0.00001)							
2 certolizumab pegol 400 mg sc							
RAPID1 2005	390	-3.4 (1.4)	99	-2.4 (1.3)		49.0 %	-1.00 [-1.29, -0.71]
Subtotal (95% CI)	**390**		**99**			**49.0 %**	**-1.00 [-1.29, -0.71]**
Heterogeneity: not applicable							
Test for overall effect: Z = 6.73 (P < 0.00001)							
Total (95% CI)	**783**		**199**			**100.0 %**	**-0.95 [-1.15, -0.75]**
Heterogeneity: Chi^2 = 0.23, df = 1 (P = 0.63); I^2 =0.0%							
Test for overall effect: Z = 9.12 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.23, df = 1 (P = 0.63), I^2 =0.0%							



Analysis 32.1. Comparison 32 DAS-28 at 24 weeks, 200 mg certolizumab, Outcome 1 DAS 28 (ESR) change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 32 DAS-28 at 24 weeks, 200 mg certolizumab

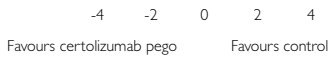
Outcome: 1 DAS 28 (ESR) change from baseline

Study or subgroup	Certolizumab pegol 200 mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID2 2007	246	-2.27 (1.38)	127	-0.5 (1.05)		100.0 %	-1.77 [-2.02, -1.52]
Total (95% CI)	**246**		**127**			**100.0 %**	**-1.77 [-2.02, -1.52]**

Heterogeneity: not applicable

Test for overall effect: Z = 13.81 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 33.1. Comparison 33 Erosion score (ES), Outcome 1 Change from the baseline mean ES at week 24, certolizumab pegol 200 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 33 Erosion score (ES)

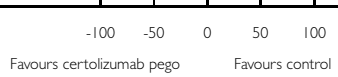
Outcome: 1 Change from the baseline mean ES at week 24, certolizumab pegol 200 mg

Study or subgroup	Certolizumab pegol 200 mg N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
RAPID1 2005	353	0 (1.5)	180	0.7 (2.1)		61.6 %	-0.41 [-0.59, -0.22]
RAPID2 2007	214	0.1 (2)	112	0.7 (2.6)		38.4 %	-0.27 [-0.50, -0.04]
Total (95% CI)	**567**		**292**			**100.0 %**	**-0.35 [-0.50, -0.21]**

Heterogeneity: Chi^2 = 0.83, df = 1 (P = 0.36); I^2 =0.0%

Test for overall effect: Z = 4.86 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 33.2. Comparison 33 Erosion score (ES), Outcome 2 Change from the baseline mean ES at week 24, certolizumab pegol 400 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 33 Erosion score (ES)

Outcome: 2 Change from the baseline mean ES at week 24, certolizumab pegol 400 mg

Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
RAPID1 2005	355	0.1 (2.4)	180	0.7 (2.1)		60.7 %	-0.60 [-1.00, -0.20]
RAPID2 2007	222	-0.3 (1.8)	112	0.7 (2.6)		39.3 %	-1.00 [-1.54, -0.46]
Total (95% CI)	**577**		**292**			**100.0 %**	**-0.76 [-1.14, -0.37]**

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 1.38$, df = 1 (P = 0.24); $I^2 = 28\%$

Test for overall effect: Z = 3.88 (P = 0.00011)

Test for subgroup differences: Not applicable

Analysis 33.3. Comparison 33 Erosion score (ES), Outcome 3 Change from the baseline mean ES at week 52, certolizumab pegol 200 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 33 Erosion score (ES)

Outcome: 3 Change from the baseline mean ES at week 52, certolizumab pegol 200 mg

Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	364	0.1 (2.5)	180	1.5 (4.3)		100.0 %	-1.40 [-2.08, -0.72]
Total (95% CI)	**364**		**180**			**100.0 %**	**-1.40 [-2.08, -0.72]**

Heterogeneity: not applicable

Test for overall effect: Z = 4.04 (P = 0.000053)

Test for subgroup differences: Not applicable

Analysis 33.4. Comparison 33 Erosion score (ES), Outcome 4 Change from the baseline mean ES at week 52, certolizumab pegol 400 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 33 Erosion score (ES)

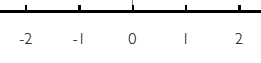
Outcome: 4 Change from the baseline mean ES at week 52, certolizumab pegol 400 mg

Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	363	0 (3)	180	1.5 (4.3)		100.0 %	-1.50 [-2.20, -0.80]
Total (95% CI)	**363**		**180**			**100.0 %**	**-1.50 [-2.20, -0.80]**

Heterogeneity: not applicable

Test for overall effect: Z = 4.20 (P = 0.000027)

Test for subgroup differences: Not applicable



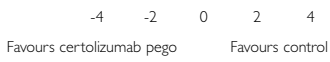
Analysis 34.1. Comparison 34 Erosion score (ES) at 24 weeks, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 34 Erosion score (ES) at 24 weeks, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 certolizumab pegol 200 mg sc							
RAPID1 2005	353	0 (1.5)	91	0.7 (2.1)		37.9 %	-0.70 [-1.16, -0.24]
RAPID2 2007	214	0.1 (2)	56	0.7 (2.6)		14.9 %	-0.60 [-1.33, 0.13]
Subtotal (95% CI)	**567**		**147**			**52.8 %**	**-0.67 [-1.06, -0.28]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.05$, df = 1 (P = 0.82); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.39 (P = 0.00071)							
2 certolizumab pegol 400 mg sc							
RAPID1 2005	355	0.1 (2.4)	90	0.7 (2.1)		31.9 %	-0.60 [-1.10, -0.10]
RAPID2 2007	222	-0.3 (1.8)	56	0.7 (2.6)		15.4 %	-1.00 [-1.72, -0.28]
Subtotal (95% CI)	**577**		**146**			**47.2 %**	**-0.73 [-1.14, -0.32]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.80$, df = 1 (P = 0.37); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.48 (P = 0.00050)							
Total (95% CI)	**1144**		**293**			**100.0 %**	**-0.70 [-0.98, -0.42]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.89$, df = 3 (P = 0.83); $I^2 = 0.0\%$							
Test for overall effect: Z = 4.85 (P < 0.00001)							
Test for subgroup differences: $Chi^2 = 0.04$, df = 1 (P = 0.84), $I^2 = 0.0\%$							



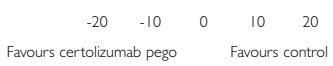
Analysis 35.1. Comparison 35 Erosion score (ES) at 52 weeks, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 35 Erosion score (ES) at 52 weeks, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 certolizumab pegol 200 mg sc							
RAPID1 2005	364	0.1 (2.5)	91	1.5 (4.3)		51.1 %	-1.40 [-2.32, -0.48]
Subtotal (95% CI)	**364**		**91**			**51.1 %**	**-1.40 [-2.32, -0.48]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.98 (P = 0.0029)							
2 certolizumab pegol 400 mg sc							
RAPID1 2005	363	0 (3)	90	1.5 (4.3)		48.9 %	-1.50 [-2.44, -0.56]
Subtotal (95% CI)	**363**		**90**			**48.9 %**	**-1.50 [-2.44, -0.56]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.13 (P = 0.0018)							
Total (95% CI)	**727**		**181**			**100.0 %**	**-1.45 [-2.11, -0.79]**
Heterogeneity: Chi^2 = 0.02, df = 1 (P = 0.88); I^2 =0.0%							
Test for overall effect: Z = 4.32 (P = 0.000016)							
Test for subgroup differences: Chi^2 = 0.02, df = 1 (P = 0.88), I^2 =0.0%							



Analysis 36.1. Comparison 36 Joint space narrowing (JSN), Outcome 1 Change from the baseline mean JSN 24 weeks, certolizumab pegol 200 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 36 Joint space narrowing (JSN)

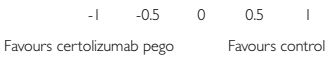
Outcome: 1 Change from the baseline mean JSN 24 weeks, certolizumab pegol 200 mg

Study or subgroup	Certolizumab pegol 200 mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
RAPID1 2005	355	0.2 (2.5)	180	0.7 (2.4)		53.2 %	-0.50 [-0.94, -0.06]
RAPID2 2007	214	0.1 (1.4)	112	0.5 (2.3)		46.8 %	-0.40 [-0.87, 0.07]
Total (95% CI)	**569**		**292**			**100.0 %**	**-0.45 [-0.77, -0.13]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.09$, df = 1 (P = 0.76); $I^2 = 0.0\%$

Test for overall effect: Z = 2.79 (P = 0.0053)

Test for subgroup differences: Not applicable



Analysis 36.2. Comparison 36 Joint space narrowing (JSN), Outcome 2 Change from the baseline mean JSN 24 weeks,certolizumab pegol 400 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 36 Joint space narrowing (JSN)

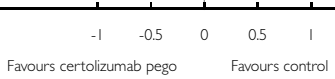
Outcome: 2 Change from the baseline mean JSN 24 weeks,certolizumab pegol 400 mg

Study or subgroup	Certolizumab pegol 400 mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
RAPID1 2005	355	0.2 (2.4)	180	0.7 (2.4)		51.8 %	-0.50 [-0.93, -0.07]
RAPID2 2007	222	-0.1 (1)	112	0.5 (2.3)		48.2 %	-0.60 [-1.05, -0.15]
Total (95% CI)	**577**		**292**			**100.0 %**	**-0.55 [-0.86, -0.24]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.10$, df = 1 (P = 0.75); $I^2 = 0.0\%$

Test for overall effect: Z = 3.47 (P = 0.00052)

Test for subgroup differences: Not applicable



Analysis 36.3. Comparison 36 Joint space narrowing (JSN), Outcome 3 Change from the baseline mean JSN 52 weeks,certolizumab pegol 200 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 36 Joint space narrowing (JSN)

Outcome: 3 Change from the baseline mean JSN 52 weeks,certolizumab pegol 200 mg

Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	367	0.4 (4.2)	181	1.4 (5)		100.0 %	-1.00 [-1.85, -0.15]
Total (95% CI)	**367**		**181**			**100.0 %**	**-1.00 [-1.85, -0.15]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.32 (P = 0.020)

Test for subgroup differences: Not applicable

Analysis 36.4. Comparison 36 Joint space narrowing (JSN), Outcome 4 Change from the baseline mean JSN 52 weeks, certolizumab pegol 400 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 36 Joint space narrowing (JSN)

Outcome: 4 Change from the baseline mean JSN 52 weeks, certolizumab pegol 400 mg

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	363	0.2 (2.8)	181	1.4 (5)		100.0 %	-1.20 [-1.98, -0.42]
Total (95% CI)	**363**		**181**			**100.0 %**	**-1.20 [-1.98, -0.42]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.00 (P = 0.0027)

Test for subgroup differences: Not applicable

Analysis 37.1. Comparison 37 Joint space narrowing (JSN) at 24 weeks, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 37 Joint space narrowing (JSN) at 24 weeks, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 certolizumab pegol 200 mg sc							
RAPID1 2005	355	0.2 (2.5)	91	0.7 (2.4)		27.7 %	-0.50 [-1.06, 0.06]
RAPID2 2007	214	0.1 (1.4)	56	0.5 (2.3)		21.6 %	-0.40 [-1.03, 0.23]
Subtotal (95% CI)	**569**		**147**			**49.4 %**	**-0.46 [-0.87, -0.04]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.05$, df = 1 (P = 0.82); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.14 (P = 0.032)							
2 certolizumab pegol 400 mg sc							
RAPID1 2005	355	0.2 (2.4)	90	0.7 (2.4)		28.0 %	-0.50 [-1.06, 0.06]
RAPID2 2007	222	-0.1 (1)	56	0.5 (2.3)		22.7 %	-0.60 [-1.22, 0.02]
Subtotal (95% CI)	**577**		**146**			**50.6 %**	**-0.54 [-0.96, -0.13]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.06$, df = 1 (P = 0.81); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.59 (P = 0.0097)							
Total (95% CI)	**1146**		**293**			**100.0 %**	**-0.50 [-0.79, -0.21]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.20$, df = 3 (P = 0.98); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.35 (P = 0.00082)							
Test for subgroup differences: $Chi^2 = 0.09$, df = 1 (P = 0.77), $I^2 = 0.0\%$							

Analysis 38.1. Comparison 38 Joint space narrowing (JSN) at 52 weeks, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 38 Joint space narrowing (JSN) at 52 weeks, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 certolizumab pegol 200 mg sc							
RAPID1 2005	367	0.4 (4.2)	91	1.4 (5)		48.1 %	-1.00 [-2.11, 0.11]
Subtotal (95% CI)	**367**		**91**			**48.1 %**	**-1.00 [-2.11, 0.11]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.76 (P = 0.078)							
2 certolizumab pegol 400 mg sc							
RAPID1 2005	363	0.2 (2.8)	90	1.4 (5)		51.9 %	-1.20 [-2.27, -0.13]
Subtotal (95% CI)	**363**		**90**			**51.9 %**	**-1.20 [-2.27, -0.13]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.19 (P = 0.028)							
Total (95% CI)	**730**		**181**			**100.0 %**	**-1.10 [-1.88, -0.33]**
Heterogeneity: Chi^2 = 0.06, df = 1 (P = 0.80); I^2 =0.0%							
Test for overall effect: Z = 2.80 (P = 0.0051)							
Test for subgroup differences: Chi^2 = 0.06, df = 1 (P = 0.80), I^2 =0.0%							

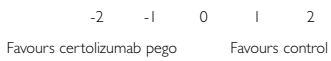
Analysis 39.1. Comparison 39 Modified Total Sharp Scores (mTSS) at 24 weeks, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 39 Modified Total Sharp Scores (mTSS) at 24 weeks, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 certolizumab pegol 200 mg sc							
RAPID1 2005	353	0.2 (3.2)	90	1.3 (3.8)		32.6 %	-1.10 [-1.95, -0.25]
RAPID2 2007	214	0.2 (2.7)	56	1.2 (4.1)		18.5 %	-1.00 [-2.13, 0.13]
Subtotal (95% CI)	**567**		**146**			**51.1 %**	**-1.06 [-1.75, -0.38]**
Heterogeneity: Tau² = 0.0; Chi² = 0.02, df = 1 (P = 0.89); I² =0.0%							
Test for overall effect: Z = 3.06 (P = 0.0022)							
2 certolizumab pegol 400 mg sc							
RAPID1 2005	355	0.2 (4.2)	91	1.3 (3.8)		29.6 %	-1.10 [-1.99, -0.21]
RAPID2 2007	222	-0.4 (2.1)	56	1.2 (4.1)		19.3 %	-1.60 [-2.71, -0.49]
Subtotal (95% CI)	**577**		**147**			**48.9 %**	**-1.30 [-1.99, -0.60]**
Heterogeneity: Tau² = 0.0; Chi² = 0.47, df = 1 (P = 0.49); I² =0.0%							
Test for overall effect: Z = 3.65 (P = 0.00026)							
Total (95% CI)	**1144**		**293**			**100.0 %**	**-1.18 [-1.67, -0.69]**
Heterogeneity: Tau² = 0.0; Chi² = 0.71, df = 3 (P = 0.87); I² =0.0%							
Test for overall effect: Z = 4.74 (P < 0.00001)							
Test for subgroup differences: Chi² = 0.22, df = 1 (P = 0.64), I² =0.0%							



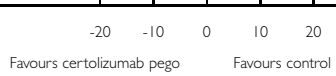
Analysis 40.1. Comparison 40 Modified Total Sharp Scores (mTSS) at 52 weeks, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 40 Modified Total Sharp Scores (mTSS) at 52 weeks, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 certolizumab pegol 200 mg sc							
RAPID1 2005	364	0.4 (5.7)	91	2.8 (7.8)		49.4 %	-2.40 [-4.11, -0.69]
Subtotal (95% CI)	**364**		**91**			**49.4 %**	**-2.40 [-4.11, -0.69]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.76 (P = 0.0058)							
2 certolizumab pegol 400 mg sc							
RAPID1 2005	363	0.2 (4.8)	90	2.8 (7.8)		50.6 %	-2.60 [-4.29, -0.91]
Subtotal (95% CI)	**363**		**90**			**50.6 %**	**-2.60 [-4.29, -0.91]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.02 (P = 0.0025)							
Total (95% CI)	**727**		**181**			**100.0 %**	**-2.50 [-3.70, -1.30]**
Heterogeneity: Chi^2 = 0.03, df = 1 (P = 0.87); I^2 =0.0%							
Test for overall effect: Z = 4.09 (P = 0.000043)							
Test for subgroup differences: Chi^2 = 0.03, df = 1 (P = 0.87), I^2 =0.0%							



Analysis 41.1. Comparison 41 Patient's assessment of arthritis pain (VAS score 0 to 100 mm), Outcome 1 Mean change at 24 weeks certolizumab pegol 200 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 41 Patient's assessment of arthritis pain (VAS score 0 to 100 mm)

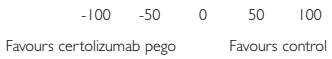
Outcome: 1 Mean change at 24 weeks certolizumab pegol 200 mg

Study or subgroup	Certolizumab pegol 200 mg N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
RAPID1 2005	393	-29.6 (21.81)	199	-8.1 (22.57)		59.7 %	-21.50 [-25.31, -17.69]
RAPID2 2007	246	-23.7 (22)	127	-4.7 (21.41)		40.3 %	-19.00 [-23.63, -14.37]
Total (95% CI)	**639**		**326**			**100.0 %**	**-20.49 [-23.43, -17.55]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.67$, df = 1 (P = 0.41); $I^2 = 0.0\%$

Test for overall effect: Z = 13.66 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 41.2. Comparison 41 Patient's assessment of arthritis pain (VAS score 0 to 100 mm), Outcome 2 Mean change at 24 weeks certolizumab pegol 400 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 41 Patient's assessment of arthritis pain (VAS score 0 to 100 mm)

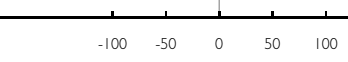
Outcome: 2 Mean change at 24 weeks certolizumab pegol 400 mg

Study or subgroup	Certolizumab pegol 400 mg N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
FAST4WARD 2005 (1)	111	-20.6 (42)	109	1.7 (42)		6.6 %	-22.30 [-33.40, -11.20]
RAPID1 2005 (2)	390	-31.7 (21.72)	199	-8.1 (22.57)		55.8 %	-23.60 [-27.41, -19.79]
RAPID2 2007	246	-26.1 (22)	127	-4.7 (21.41)		37.7 %	-21.40 [-26.03, -16.77]
Total (95% CI)	**747**		**435**			**100.0 %**	**-22.69 [-25.53, -19.84]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.52$, df = 2 (P = 0.77); $I^2 = 0.0\%$

Test for overall effect: Z = 15.65 (P < 0.00001)

Test for subgroup differences: Not applicable



(1) In FAST4WARD we have obtained standard deviations from p values according to the Handbook section 7.7.3.7

(2) Data in RAPID1 from NICE report

Analysis 41.3. Comparison 41 Patient's assessment of arthritis pain (VAS score 0 to 100 mm), Outcome 3 Mean change at 52 weeks certolizumab pegol 200 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 41 Patient's assessment of arthritis pain (VAS score 0 to 100 mm)

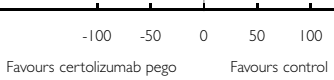
Outcome: 3 Mean change at 52 weeks certolizumab pegol 200 mg

Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	393	-31 (22.57)	199	-8.8 (23.79)		100.0 %	-22.20 [-26.19, -18.21]
Total (95% CI)	**393**		**199**			**100.0 %**	**-22.20 [-26.19, -18.21]**

Heterogeneity: not applicable

Test for overall effect: Z = 10.91 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 41.4. Comparison 41 Patient's assessment of arthritis pain (VAS score 0 to 100 mm), Outcome 4 Mean change at 52 weeks certolizumab pegol 400 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 41 Patient's assessment of arthritis pain (VAS score 0 to 100 mm)

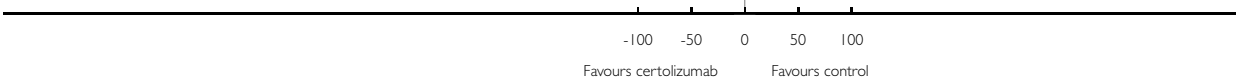
Outcome: 4 Mean change at 52 weeks certolizumab pegol 400 mg

Study or subgroup	Certolizumab N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	390	-33.5 (23.7)	199	-8.8 (22.57)		100.0 %	-24.70 [-28.62, -20.78]
Total (95% CI)	**390**		**199**			**100.0 %**	**-24.70 [-28.62, -20.78]**

Heterogeneity: not applicable

Test for overall effect: Z = 12.35 (P < 0.00001)

Test for subgroup differences: Not applicable



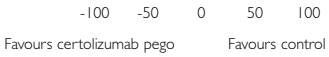
Analysis 42.1. Comparison 42 Patient's assessment of arthritis pain (VAS score 0 to 100 mm) at 24 weeks, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 42 Patient's assessment of arthritis pain (VAS score 0 to 100 mm) at 24 weeks, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 certolizumab pegol 200 mg sc							
RAPID1 2005 (1)	393	-29.6 (21.81)	100	-8.1 (22.57)		26.2 %	-21.50 [-26.42, -16.58]
RAPID2 2007	246	-23.7 (22)	64	-4.7 (21.41)		18.1 %	-19.00 [-24.92, -13.08]
Subtotal (95% CI)	**639**		**164**			**44.3 %**	**-20.48 [-24.26, -16.69]**
Heterogeneity: Tau² = 0.0; Chi² = 0.40, df = 1 (P = 0.52); I² =0.0%							
Test for overall effect: Z = 10.60 (P < 0.00001)							
2 certolizumab pegol 400 mg sc							
CDP870-014 2009 (2)	124	-21.8 (51.4)	119	-8.5 (19.92)		6.7 %	-13.30 [-23.03, -3.57]
FAST4WARD 2005	111	-20.6 (42)	109	1.7 (42)		5.1 %	-22.30 [-33.40, -11.20]
RAPID1 2005	390	-31.7 (21.72)	99	-8.1 (22.57)		26.0 %	-23.60 [-28.54, -18.66]
RAPID2 2007	246	-26.1 (22)	63	-4.7 (21.41)		17.9 %	-21.40 [-27.36, -15.44]
Subtotal (95% CI)	**871**		**390**			**55.7 %**	**-21.35 [-25.08, -17.61]**
Heterogeneity: Tau² = 2.00; Chi² = 3.44, df = 3 (P = 0.33); I² =13%							
Test for overall effect: Z = 11.20 (P < 0.00001)							
Total (95% CI)	**1510**		**554**			**100.0 %**	**-21.07 [-23.59, -18.55]**
Heterogeneity: Tau² = 0.0; Chi² = 4.01, df = 5 (P = 0.55); I² =0.0%							
Test for overall effect: Z = 16.39 (P < 0.00001)							
Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.75), I² =0.0%							



(1) Data in RAPID1 from NICE report

(2) Calculating SD according to Handbook from p values

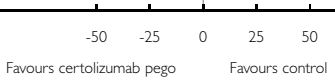
Analysis 43.1. Comparison 43 Patient's assessment of arthritis pain (VAS score 0 to 100 mm) at 52 weeks, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 43 Patient's assessment of arthritis pain (VAS score 0 to 100 mm) at 52 weeks, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 certolizumab pegol 200 mg sc							
RAPID1 2005 (1)	393	-31 (22.57)	100	-8.8 (23.79)		48.6 %	-22.20 [-27.37, -17.03]
Subtotal (95% CI)	**393**		**100**			**48.6 %**	**-22.20 [-27.37, -17.03]**
Heterogeneity: not applicable							
Test for overall effect: Z = 8.42 (P < 0.00001)							
2 certolizumab pegol 400 mg sc							
RAPID1 2005	390	-33.5 (23.7)	99	-8.8 (22.57)		51.4 %	-24.70 [-29.73, -19.67]
Subtotal (95% CI)	**390**		**99**			**51.4 %**	**-24.70 [-29.73, -19.67]**
Heterogeneity: not applicable							
Test for overall effect: Z = 9.62 (P < 0.00001)							
Total (95% CI)	**783**		**199**			**100.0 %**	**-23.48 [-27.09, -19.88]**
Heterogeneity: Chi^2 = 0.46, df = 1 (P = 0.50); I^2 =0.0%							
Test for overall effect: Z = 12.77 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.46, df = 1 (P = 0.50), I^2 =0.0%							



(1) Data in RAPID1 from NICE report

Analysis 44.1. Comparison 44 Modified total Sharp scores (mTSS), Outcome 1 Change from the baseline mean mTSS 24 weeks, certolizumab pegol 200 mg..

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 44 Modified total Sharp scores (mTSS)

Outcome: 1 Change from the baseline mean mTSS 24 weeks, certolizumab pegol 200 mg.

Study or subgroup	Certolizumab pegol 200 mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
RAPID1 2005	353	0.2 (3.2)	180	1.3 (3.8)		62.8 %	-1.10 [-1.75, -0.45]
RAPID2 2007	214	0.2 (2.7)	112	1.2 (4.1)		37.2 %	-1.00 [-1.84, -0.16]
Total (95% CI)	**567**		**292**			**100.0 %**	**-1.06 [-1.58, -0.55]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.03$, df = 1 (P = 0.85); $I^2 = 0.0\%$

Test for overall effect: Z = 4.06 (P = 0.000049)

Test for subgroup differences: Not applicable

Analysis 44.2. Comparison 44 Modified total Sharp scores (mTSS), Outcome 2 Change from the baseline mean mTSS 24 weeks, certolizumab 400 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 44 Modified total Sharp scores (mTSS)

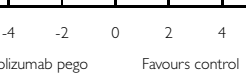
Outcome: 2 Change from the baseline mean mTSS 24 weeks, certolizumab 400 mg

Study or subgroup	Certolizumab pegol 400 mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
RAPID1 2005	355	0.2 (4.2)	180	1.3 (3.8)		56.7 %	-1.10 [-1.81, -0.39]
RAPID2 2007	222	-0.4 (2.1)	112	1.2 (4.1)		43.3 %	-1.60 [-2.41, -0.79]
Total (95% CI)	**577**		**292**			**100.0 %**	**-1.32 [-1.85, -0.78]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.83$, df = 1 (P = 0.36); $I^2 = 0.0\%$

Test for overall effect: Z = 4.85 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 44.3. Comparison 44 Modified total Sharp scores (mTSS), Outcome 3 Change from the baseline mean mTSS 52 weeks, certolizumab pegol 200 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 44 Modified total Sharp scores (mTSS)

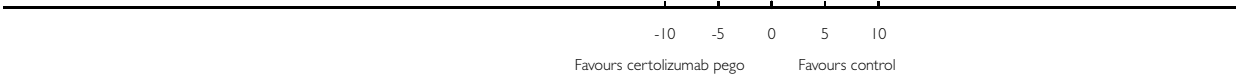
Outcome: 3 Change from the baseline mean mTSS 52 weeks, certolizumab pegol 200 mg

Study or subgroup	Certolizumab pegol 200mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	364	0.4 (5.7)	181	2.8 (7.8)		100.0 %	-2.40 [-3.68, -1.12]
Total (95% CI)	**364**		**181**			**100.0 %**	**-2.40 [-3.68, -1.12]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.68 (P = 0.00023)

Test for subgroup differences: Not applicable



Analysis 44.4. Comparison 44 Modified total Sharp scores (mTSS), Outcome 4 Change from the baseline mean mTSS 52 weeks, certolizumab pegol 400 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 44 Modified total Sharp scores (mTSS)

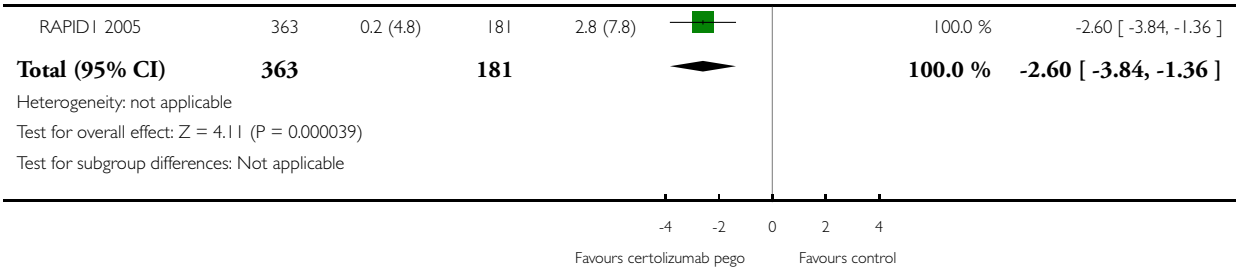
Outcome: 4 Change from the baseline mean mTSS 52 weeks, certolizumab pegol 400 mg

Study or subgroup	Certolizumab pegol 400 mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	363	0.2 (4.8)	181	2.8 (7.8)		100.0 %	-2.60 [-3.84, -1.36]
Total (95% CI)	**363**		**181**			**100.0 %**	**-2.60 [-3.84, -1.36]**

Heterogeneity: not applicable

Test for overall effect: Z = 4.11 (P = 0.000039)

Test for subgroup differences: Not applicable



Analysis 45.1. Comparison 45 Certolizumab pegol 1mg/kg/day sc, Outcome 1 Headache.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 45 Certolizumab pegol 1mg/kg/day sc

Outcome: 1 Headache

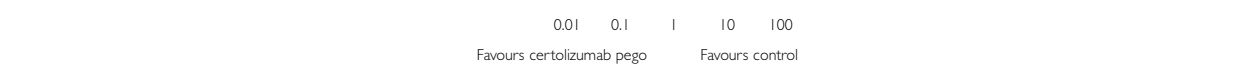
Study or subgroup	certolizumab pegol 1 mg n/N	control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Choy 2002	3/8	1/12		100.0 %	4.50 [0.56, 35.98]
Total (95% CI)	**8**	**12**		**100.0 %**	**4.50 [0.56, 35.98]**

Total events: 3 (certolizumab pegol 1 mg), 1 (control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.42 (P = 0.16)

Test for subgroup differences: Not applicable

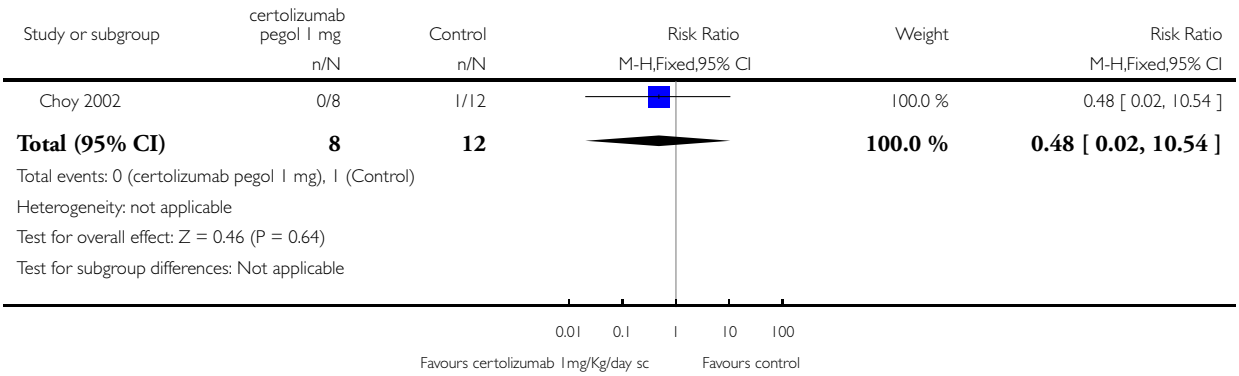


Analysis 45.2. Comparison 45 Certolizumab pegol 1mg/kg/day sc, Outcome 2 Lower respiratory tract infection.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 45 Certolizumab pegol 1mg/kg/day sc

Outcome: 2 Lower respiratory tract infection

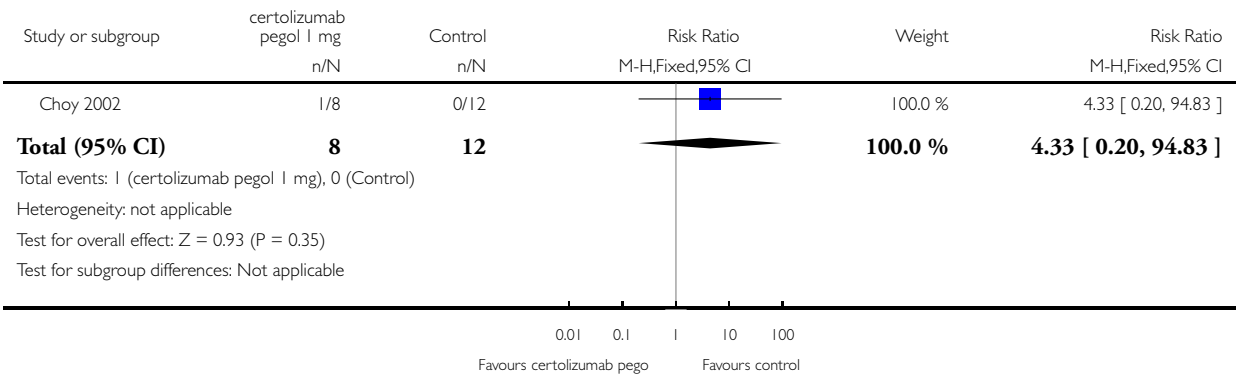


Analysis 45.3. Comparison 45 Certolizumab pegol 1mg/kg/day sc, Outcome 3 Adverse events Intensity severe.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 45 Certolizumab pegol 1mg/kg/day sc

Outcome: 3 Adverse events Intensity severe



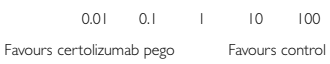
Analysis 45.4. Comparison 45 Certolizumab pegol 1mg/kg/day sc, Outcome 4 Antinuclear antibodies (ANA).

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 45 Certolizumab pegol 1mg/kg/day sc

Outcome: 4 Antinuclear antibodies (ANA)

Study or subgroup	certolizumab pegol 1 mg n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Choy 2002	2/8	1/12		100.0 %	3.00 [0.32, 27.83]
Total (95% CI)	**8**	**12**		**100.0 %**	**3.00 [0.32, 27.83]**
Total events: 2 (certolizumab pegol 1 mg), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.97 (P = 0.33)					
Test for subgroup differences: Not applicable					



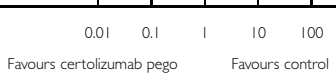
Analysis 45.5. Comparison 45 Certolizumab pegol 1mg/kg/day sc, Outcome 5 Urinary tract infection.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 45 Certolizumab pegol 1mg/kg/day sc

Outcome: 5 Urinary tract infection

Study or subgroup	certolizumab pegol 1 mg n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Choy 2002	1/8	0/12		100.0 %	4.33 [0.20, 94.83]
Total (95% CI)	**8**	**12**		**100.0 %**	**4.33 [0.20, 94.83]**
Total events: 1 (certolizumab pegol 1 mg), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.93 (P = 0.35)					
Test for subgroup differences: Not applicable					

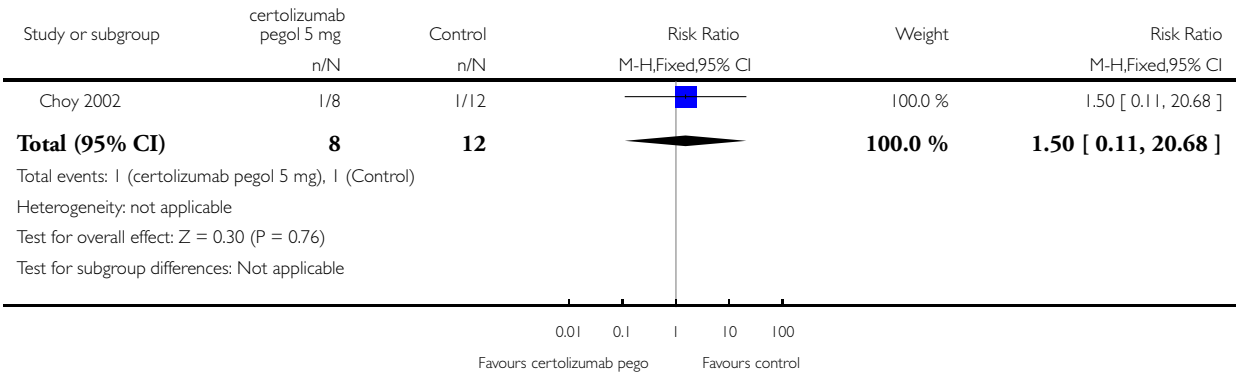


Analysis 46.1. Comparison 46 Certolizumab 5 mg/kg/day sc, Outcome 1 Lower respiratory tract infection.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 46 Certolizumab 5 mg/kg/day sc

Outcome: 1 Lower respiratory tract infection

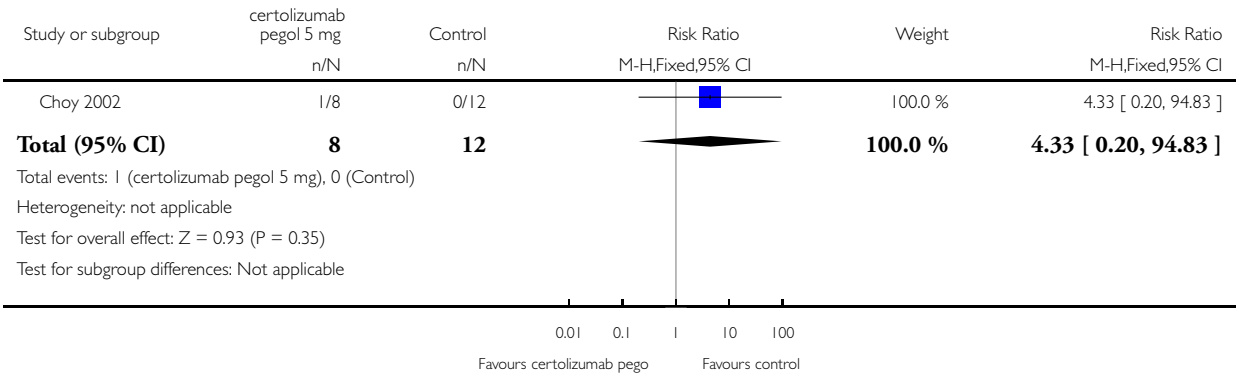


Analysis 46.2. Comparison 46 Certolizumab 5 mg/kg/day sc, Outcome 2 Urinary tract infection.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 46 Certolizumab 5 mg/kg/day sc

Outcome: 2 Urinary tract infection



Analysis 47.1. Comparison 47 Certolizumab 20 mg/kg/day sc, Outcome 1 Headache.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 47 Certolizumab 20 mg/kg/day sc

Outcome: 1 Headache

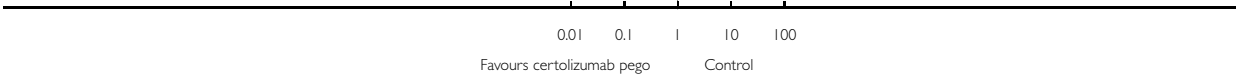
Study or subgroup	certolizumab pegol 20 mg n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Choy 2002	3/8	1/12		100.0 %	4.50 [0.56, 35.98]
Total (95% CI)	**8**	**12**		**100.0 %**	**4.50 [0.56, 35.98]**

Total events: 3 (certolizumab pegol 20 mg), 1 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.42 (P = 0.16)

Test for subgroup differences: Not applicable



Analysis 47.2. Comparison 47 Certolizumab 20 mg/kg/day sc, Outcome 2 Lower respiratory tract infection.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 47 Certolizumab 20 mg/kg/day sc

Outcome: 2 Lower respiratory tract infection

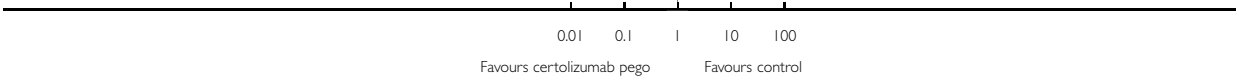
Study or subgroup	certolizumab pegol 20 mg n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Choy 2002	2/8	1/12		100.0 %	3.00 [0.32, 27.83]
Total (95% CI)	**8**	**12**		**100.0 %**	**3.00 [0.32, 27.83]**

Total events: 2 (certolizumab pegol 20 mg), 1 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.97 (P = 0.33)

Test for subgroup differences: Not applicable



Analysis 47.3. Comparison 47 Certolizumab 20 mg/kg/day sc, Outcome 3 Death.

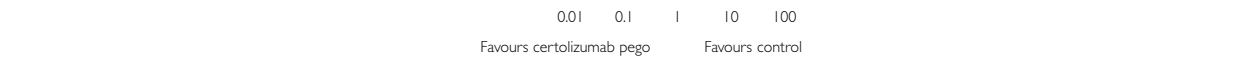
Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 47 Certolizumab 20 mg/kg/day sc

Outcome: 3 Death

Study or subgroup	certolizumab pegol 20 mg n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Choy 2002	1/8	0/12		100.0 %	4.33 [0.20, 94.83]
Total (95% CI)	**8**	**12**		**100.0 %**	**4.33 [0.20, 94.83]**

Total events: 1 (certolizumab pegol 20 mg), 0 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.93 (P = 0.35)
Test for subgroup differences: Not applicable



Analysis 47.4. Comparison 47 Certolizumab 20 mg/kg/day sc, Outcome 4 Antinuclear antibodies (ANA).

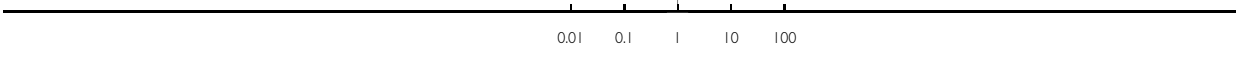
Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 47 Certolizumab 20 mg/kg/day sc

Outcome: 4 Antinuclear antibodies (ANA)

Study or subgroup	certolizumab pegol 20 mg n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Choy 2002	1/8	1/12		100.0 %	1.50 [0.11, 20.68]
Total (95% CI)	**8**	**12**		**100.0 %**	**1.50 [0.11, 20.68]**

Total events: 1 (certolizumab pegol 20 mg), 1 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.30 (P = 0.76)
Test for subgroup differences: Not applicable

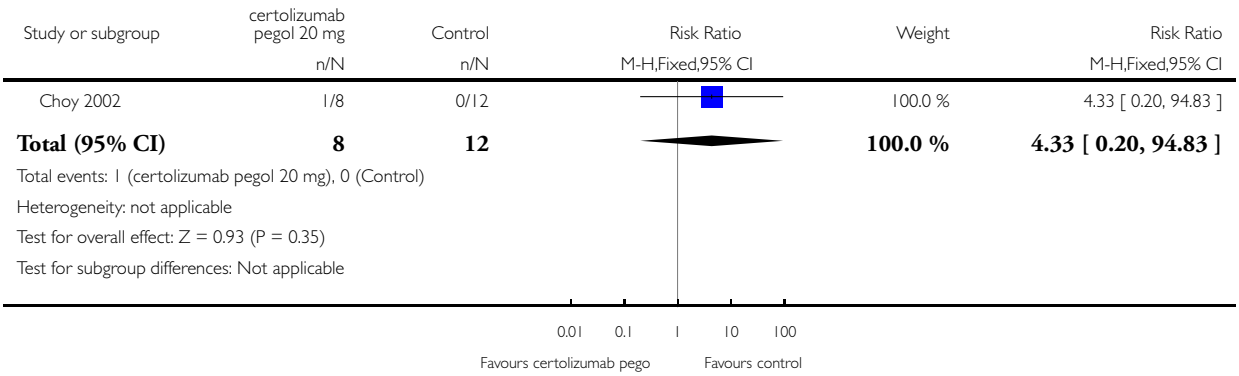


Analysis 47.5. Comparison 47 Certolizumab 20 mg/kg/day sc, Outcome 5 Urinary tract infection.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 47 Certolizumab 20 mg/kg/day sc

Outcome: 5 Urinary tract infection



Analysis 48.1. Comparison 48 Withdrawals, Outcome 1 All Withdrawn: any doses any follow up.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 48 Withdrawals

Outcome: 1 All Withdrawn: any doses any follow up

Study or subgroup	certolizumab pegol n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
CDP870-014 2009	28/126	56/121		9.5 %	0.48 [0.33, 0.70]
CERTAIN 2008	12/96	18/98		4.6 %	0.68 [0.35, 1.34]
Choy 2002	2/24	6/12		1.3 %	0.17 [0.04, 0.71]
FAST4WARD 2005	35/111	81/109		11.8 %	0.42 [0.32, 0.57]
NCT00791921 HIKARI	34/116	96/114		11.9 %	0.35 [0.26, 0.47]
NCT00791999 JRAPID (1)	36/167	52/77		10.9 %	0.32 [0.23, 0.44]
NCT00993317	25/85	21/42		8.0 %	0.59 [0.38, 0.92]
RAPID1 2005	254/783	156/199		17.0 %	0.41 [0.37, 0.47]
RAPID2 2007	137/492	110/127		16.1 %	0.32 [0.27, 0.38]
REALISTIC 2008	80/851	28/212		9.0 %	0.71 [0.48, 1.07]
Total (95% CI)	**2851**	**1111**		**100.0 %**	**0.42 [0.36, 0.50]**

Total events: 643 (certolizumab pegol), 624 (Control)

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 26.60$, df = 9 (P = 0.002); $I^2 = 66\%$

Test for overall effect: Z = 10.16 (P < 0.00001)

Test for subgroup differences: Not applicable

(1) Only for 200 and 400 mg of CTZ

Analysis 48.2. Comparison 48 Withdrawals, Outcome 2 Withdrawn due to lack of efficacy: any doses any follow up.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 48 Withdrawals

Outcome: 2 Withdrawn due to lack of efficacy: any doses any follow up

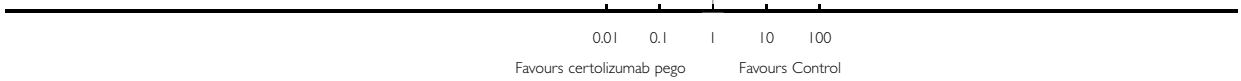
Study or subgroup	certolizumab pegol n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
CDP870-014 2009	16/126	45/121		10.8 %	0.34 [0.20, 0.57]
FAST4WARD 2005	24/111	75/109		16.6 %	0.31 [0.22, 0.46]
NCT00993317	18/85	18/42		10.0 %	0.49 [0.29, 0.85]
RAPID1 2005	151/783	125/199		32.4 %	0.31 [0.26, 0.37]
RAPID2 2007	95/492	101/127		30.2 %	0.24 [0.20, 0.30]
Total (95% CI)	**1597**	**598**		**100.0 %**	**0.30 [0.25, 0.37]**

Total events: 304 (certolizumab pegol), 364 (Control)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 7.90$, df = 4 (P = 0.10); $I^2 = 49\%$

Test for overall effect: Z = 12.04 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 48.3. Comparison 48 Withdrawals, Outcome 3 Withdrawals due to adverse events.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 48 Withdrawals

Outcome: 3 Withdrawals due to adverse events

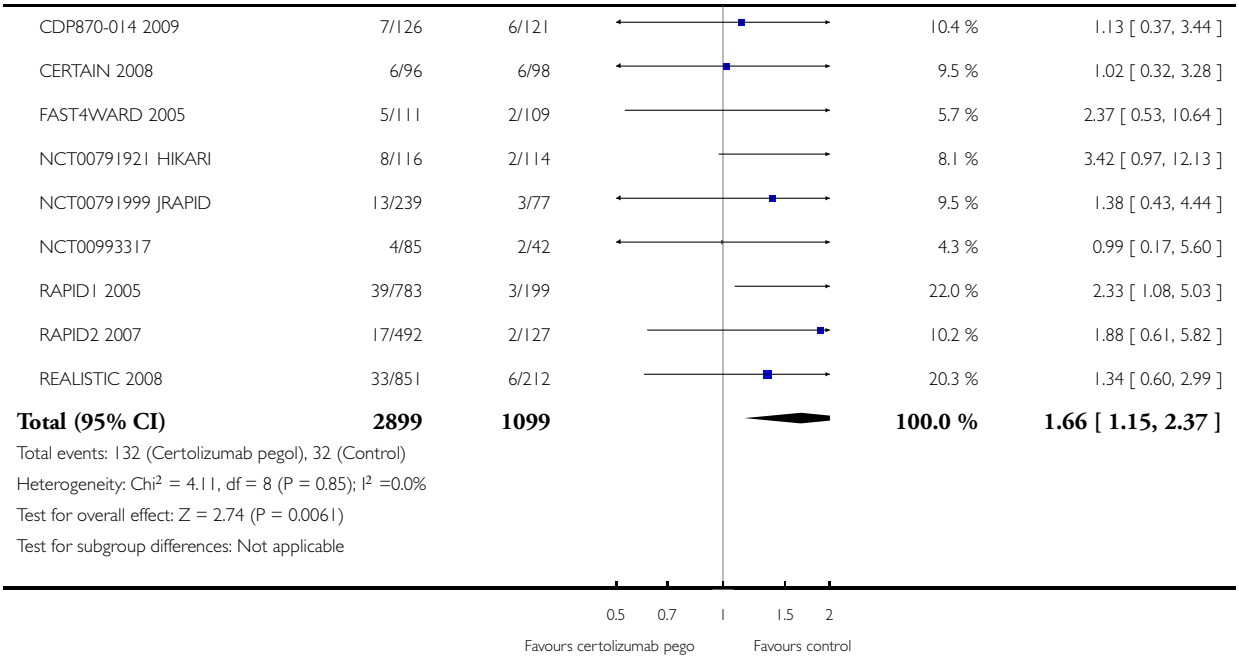
Study or subgroup	Certolizumab pegol n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CDP870-014 2009	7/126	6/121		10.4 %	1.13 [0.37, 3.44]
CERTAIN 2008	6/96	6/98		9.5 %	1.02 [0.32, 3.28]
FAST4WARD 2005	5/111	2/109		5.7 %	2.37 [0.53, 10.64]
NCT00791921 HIKARI	8/116	2/114		8.1 %	3.42 [0.97, 12.13]
NCT00791999 JRAPID	13/239	3/77		9.5 %	1.38 [0.43, 4.44]
NCT00993317	4/85	2/42		4.3 %	0.99 [0.17, 5.60]
RAPID1 2005	39/783	3/199		22.0 %	2.33 [1.08, 5.03]
RAPID2 2007	17/492	2/127		10.2 %	1.88 [0.61, 5.82]
REALISTIC 2008	33/851	6/212		20.3 %	1.34 [0.60, 2.99]
Total (95% CI)	**2899**	**1099**		**100.0 %**	**1.66 [1.15, 2.37]**

Total events: 132 (Certolizumab pegol), 32 (Control)

Heterogeneity: $Chi^2 = 4.11$, df = 8 (P = 0.85); $I^2 = 0.0\%$

Test for overall effect: Z = 2.74 (P = 0.0061)

Test for subgroup differences: Not applicable



Analysis 49.1. Comparison 49 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 1 ACR 50 200 mg certolizumab 24 weeks.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 49 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX)

Outcome: 1 ACR 50 200 mg certolizumab 24 weeks

Study or subgroup	Certolizumab pegol 200 mg n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
CERTAIN 2008	20/96	7/98		16.7 %	2.92 [1.29, 6.58]
NCT00791999 JRAPID	45/82	13/77		24.4 %	3.25 [1.91, 5.54]
NCT00993317	35/85	8/42		20.2 %	2.16 [1.10, 4.24]
RAPID1 2005	144/393	15/199		25.3 %	4.86 [2.94, 8.04]
RAPID2 2007	80/246	4/127		13.4 %	10.33 [3.87, 27.54]
Total (95% CI)	**902**	**543**		**100.0 %**	**3.80 [2.42, 5.95]**
Total events: 324 (Certolizumab pegol 200 mg), 47 (Placebo)					
Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 9.05$, df = 4 (P = 0.06); $I^2 = 56\%$					
Test for overall effect: Z = 5.82 (P < 0.00001)					
Test for subgroup differences: Not applicable					

Analysis 49.2. Comparison 49 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 2 HAQ change from baseline 200 mg certolizumab 24 weeks.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 49 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX)

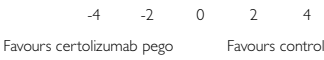
Outcome: 2 HAQ change from baseline 200 mg certolizumab 24 weeks

Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
CERTAIN 2008	91	-0.25 (0.46)	91	-0.03 (0.49)		22.8 %	-0.22 [-0.36, -0.08]
NCT00993317	81	-0.54 (0.51)	40	-0.17 (0.7)		9.6 %	-0.37 [-0.61, -0.13]
RAPID1 2005	393	-0.58 (0.59)	199	-0.17 (0.56)		33.9 %	-0.41 [-0.51, -0.31]
RAPID2 2007	246	-0.5 (0.47)	127	-0.14 (0.45)		33.7 %	-0.36 [-0.46, -0.26]
Total (95% CI)	**811**		**457**			**100.0 %**	**-0.35 [-0.43, -0.26]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.92$, df = 3 (P = 0.18); $I^2 = 39\%$

Test for overall effect: Z = 8.32 (P < 0.00001)

Test for subgroup differences: Not applicable



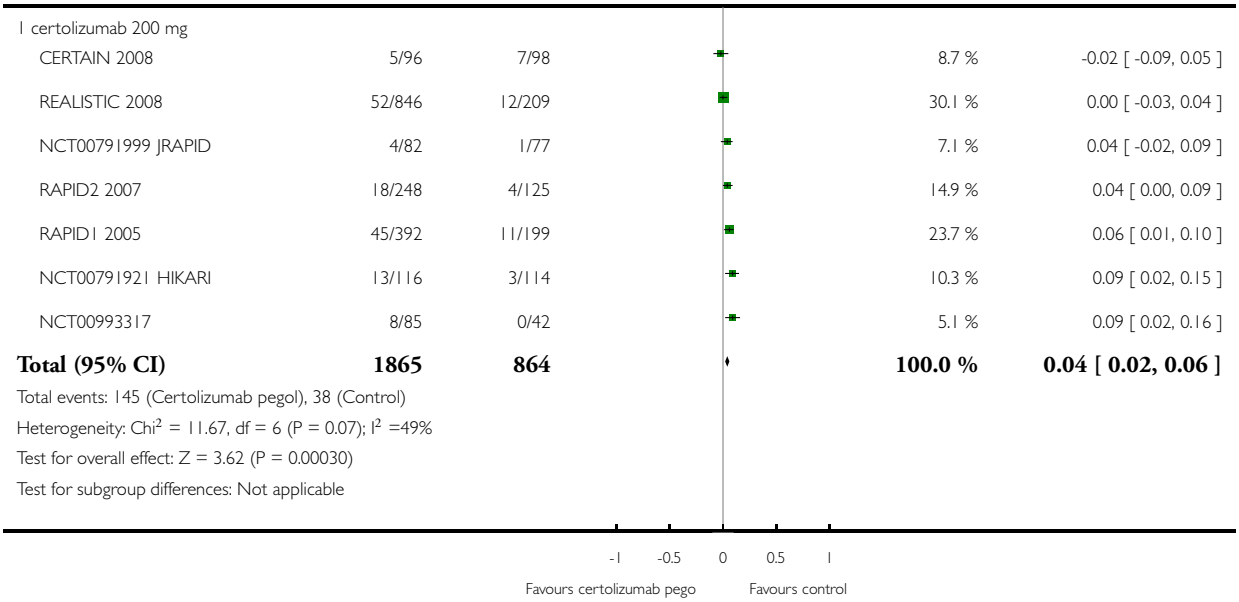
Analysis 49.3. Comparison 49 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 3 Serious adverse events certolizumab 200 mg sc.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 49 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX)

Outcome: 3 Serious adverse events certolizumab 200 mg sc

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
1 certolizumab 200 mg					
CERTAIN 2008	5/96	7/98		8.7 %	-0.02 [-0.09, 0.05]
REALISTIC 2008	52/846	12/209		30.1 %	0.00 [-0.03, 0.04]
NCT00791999 JRAPID	4/82	1/77		7.1 %	0.04 [-0.02, 0.09]
RAPID2 2007	18/248	4/125		14.9 %	0.04 [0.00, 0.09]
RAPID1 2005	45/392	11/199		23.7 %	0.06 [0.01, 0.10]
NCT00791921 HIKARI	13/116	3/114		10.3 %	0.09 [0.02, 0.15]
NCT00993317	8/85	0/42		5.1 %	0.09 [0.02, 0.16]
Total (95% CI)	**1865**	**864**		**100.0 %**	**0.04 [0.02, 0.06]**
Total events: 145 (Certolizumab pegol), 38 (Control)					
Heterogeneity: Chi^2 = 11.67, df = 6 (P = 0.07); I^2 =49%					
Test for overall effect: Z = 3.62 (P = 0.00030)					
Test for subgroup differences: Not applicable					



Analysis 49.4. Comparison 49 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 4 Proportion of patients achieving remission 24 weeks certolizumab 200 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 49 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX)

Outcome: 4 Proportion of patients achieving remission 24 weeks certolizumab 200 mg

Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
CERTAIN 2008	19/96	3/98		36.3 %	6.47 [1.98, 21.14]
NCT00791921 HIKARI	19/116	1/114		12.8 %	18.67 [2.54, 137.17]
RAPID1 2005 (1)	45/391	3/196		38.1 %	7.52 [2.37, 23.89]
RAPID2 2007 (2)	23/245	1/125		12.8 %	11.73 [1.60, 85.89]
Total (95% CI)	**848**	**533**		**100.0 %**	**8.47 [4.15, 17.28]**
Total events: 106 (Certolizumab pegol 200 mg), 8 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.97$, df = 3 (P = 0.81); $I^2 = 0.0\%$					
Test for overall effect: Z = 5.87 (P < 0.00001)					
Test for subgroup differences: Not applicable					

(1) UCB report for NICE quote Certolizumab n=391

(2) UCB report for NICE quote Certolizumab n=245

Analysis 49.5. Comparison 49 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 5 Radiological changes: Erosion Scores (ES) certolizumab 200 mg sc.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 49 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX)

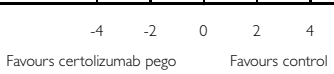
Outcome: 5 Radiological changes: Erosion Scores (ES) certolizumab 200 mg sc

Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 certolizumab 200 mg sc 24 weeks							
RAPID1 2005	353	0 (1.5)	180	0.7 (2.1)		71.9 %	-0.70 [-1.04, -0.36]
RAPID2 2007	214	0.1 (2)	112	0.7 (2.6)		28.1 %	-0.60 [-1.15, -0.05]
Total (95% CI)	**567**		**292**			**100.0 %**	**-0.67 [-0.96, -0.38]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.09$, df = 1 (P = 0.76); $I^2 = 0.0\%$

Test for overall effect: Z = 4.51 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 49.6. Comparison 49 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 6 All Withdrawals:.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 49 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX)

Outcome: 6 All Withdrawals:

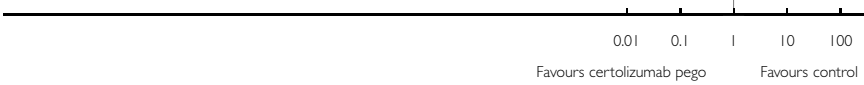
Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Choy 2002	2/24	6/12		1.3 %	0.17 [0.04, 0.71]
NCT00791999 JRAPID (1)	36/167	52/77		10.9 %	0.32 [0.23, 0.44]
RAPID2 2007	137/492	110/127		16.1 %	0.32 [0.27, 0.38]
NCT00791921 HIKARI	34/116	96/114		11.9 %	0.35 [0.26, 0.47]
RAPID1 2005	254/783	156/199		17.0 %	0.41 [0.37, 0.47]
FAST4WARD 2005	35/111	81/109		11.8 %	0.42 [0.32, 0.57]
CDP870-014 2009	28/126	56/121		9.5 %	0.48 [0.33, 0.70]
NCT00993317	25/85	21/42		8.0 %	0.59 [0.38, 0.92]
CERTAIN 2008	12/96	18/98		4.6 %	0.68 [0.35, 1.34]
REALISTIC 2008	80/851	28/212		9.0 %	0.71 [0.48, 1.07]
Total (95% CI)	**2851**	**1111**		**100.0 %**	**0.42 [0.36, 0.50]**

Total events: 643 (Certolizumab pegol), 624 (Control)

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 26.60$, df = 9 (P = 0.002); $I^2 = 66\%$

Test for overall effect: Z = 10.16 (P < 0.00001)

Test for subgroup differences: Not applicable



(1) Only for 200 and 400 mg of CTZ

Analysis 49.7. Comparison 49 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 7 Withdrawals due to adverse events.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 49 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX)

Outcome: 7 Withdrawals due to adverse events

Study or subgroup	Certolizumab pegol n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CDP870-014 2009	7/126	6/121		10.4 %	1.13 [0.37, 3.44]
CERTAIN 2008	6/96	6/98		9.5 %	1.02 [0.32, 3.28]
FAST4WARD 2005	5/111	2/109		5.7 %	2.37 [0.53, 10.64]
NCT00791921 HIKARI	8/116	2/114		8.1 %	3.42 [0.97, 12.13]
NCT00791999 JRAPID	13/239	3/77		9.5 %	1.38 [0.43, 4.44]
NCT00993317	4/85	2/42		4.3 %	0.99 [0.17, 5.60]
RAPID1 2005	39/783	3/199		22.0 %	2.33 [1.08, 5.03]
RAPID2 2007	17/492	2/127		10.2 %	1.88 [0.61, 5.82]
REALISTIC 2008	33/851	6/212		20.3 %	1.34 [0.60, 2.99]
Total (95% CI)	**2899**	**1099**		**100.0 %**	**1.66 [1.15, 2.37]**

Total events: 132 (Certolizumab pegol), 32 (Control)

Heterogeneity: $Chi^2 = 4.11$, df = 8 (P = 0.85); $I^2 = 0.0\%$

Test for overall effect: Z = 2.74 (P = 0.0061)

Test for subgroup differences: Not applicable

Analysis 49.8. Comparison 49 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 8 Deaths.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 49 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX)

Outcome: 8 Deaths

Study or subgroup	Certolizumab pegol n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Certolizumab pegol 200 mg					
CERTAIN 2008	0/96	0/98			Not estimable
NCT00791921 HIKARI (1)	1/116	0/114		10.4 %	7.26 [0.14, 366.07]
NCT00791999 JRAPID	0/82	0/25			Not estimable
RAPID1 2005 (2)	3/392	1/100		26.8 %	0.75 [0.07, 8.60]
RAPID2 2007 (3)	1/246	0/63		6.8 %	3.51 [0.03, 455.29]
REALISTIC 2008 (4)	2/846	0/209		13.2 %	3.48 [0.11, 112.96]
Subtotal (95% CI)	**1778**	**609**		**57.2 %**	**1.94 [0.36, 10.32]**
Total events: 7 (Certolizumab pegol), 1 (Placebo)					
Heterogeneity: Chi² = 1.19, df = 3 (P = 0.76); I² =0.0%					
Test for overall effect: Z = 0.78 (P = 0.44)					
2 Certolizumab pegol 400 mg					
CDP870-014 2009	0/124	0/119			Not estimable
FAST4WARD 2005	0/111	0/109			Not estimable
NCT00791999 JRAPID	0/65	0/25			Not estimable
RAPID1 2005 (5)	4/389	0/99		26.8 %	3.53 [0.31, 40.72]
RAPID2 2007 (6)	1/246	0/62		6.7 %	3.50 [0.03, 464.09]
Subtotal (95% CI)	**935**	**414**		**33.5 %**	**3.53 [0.40, 31.39]**
Total events: 5 (Certolizumab pegol), 0 (Placebo)					
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² =0.0%					
Test for overall effect: Z = 1.13 (P = 0.26)					
3 Other doses					
Choy 2002	1/24	0/12		9.3 %	4.48 [0.07, 286.49]
NCT00791999 JRAPID	0/72	0/22			Not estimable
Subtotal (95% CI)	**96**	**34**		**9.3 %**	**4.48 [0.07, 286.49]**
Total events: 1 (Certolizumab pegol), 0 (Placebo)					
Heterogeneity: not applicable					

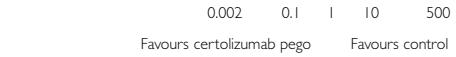
period). In Placebo 1 death (myocardial necrosis)

to CZP

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Certolizumab pegol n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Test for overall effect: Z = 0.71 (P = 0.48)					
Total (95% CI)	**2809**	**1057**		**100.0 %**	**2.56 [0.72, 9.07]**
Total events: 13 (Certolizumab pegol), 1 (Placebo)					
Heterogeneity: Chi^2 = 1.45, df = 6 (P = 0.96); I^2 =0.0%					
Test for overall effect: Z = 1.46 (P = 0.15)					
Test for subgroup differences: Chi^2 = 0.26, df = 2 (P = 0.88), I^2 =0.0%					



period). In Placebo 1 death (myocardial necrosis)

to CZP

(1) 1 patient died of a rupture of a dissecting aortic aneurysm in the thoracic region, but UCB considered that in unlikely to have beeen related to study medication

(2) Two deaths: one patient (hepatic neoplasm), and the other (cardiac arrest). One more died (peritonitis, cirrhosis, and general deterioration of physical health during the posttreatment

(3) 1 patient died by myocardial infarction

(4) Two deaths in the CZP group: one case of sigmoid diverticulitis in a 73-year-old man with pancreatitis, and one of necrotizing pneumonia, both deaths were ruled as possibly related

(5) Four deaths: 1 patient (cerebral stroke, 1 myocardial necrosis, 1 by cardiac arrest and 1 more by atrial fibrillation)

(6) 1 patient died by fracture and shock

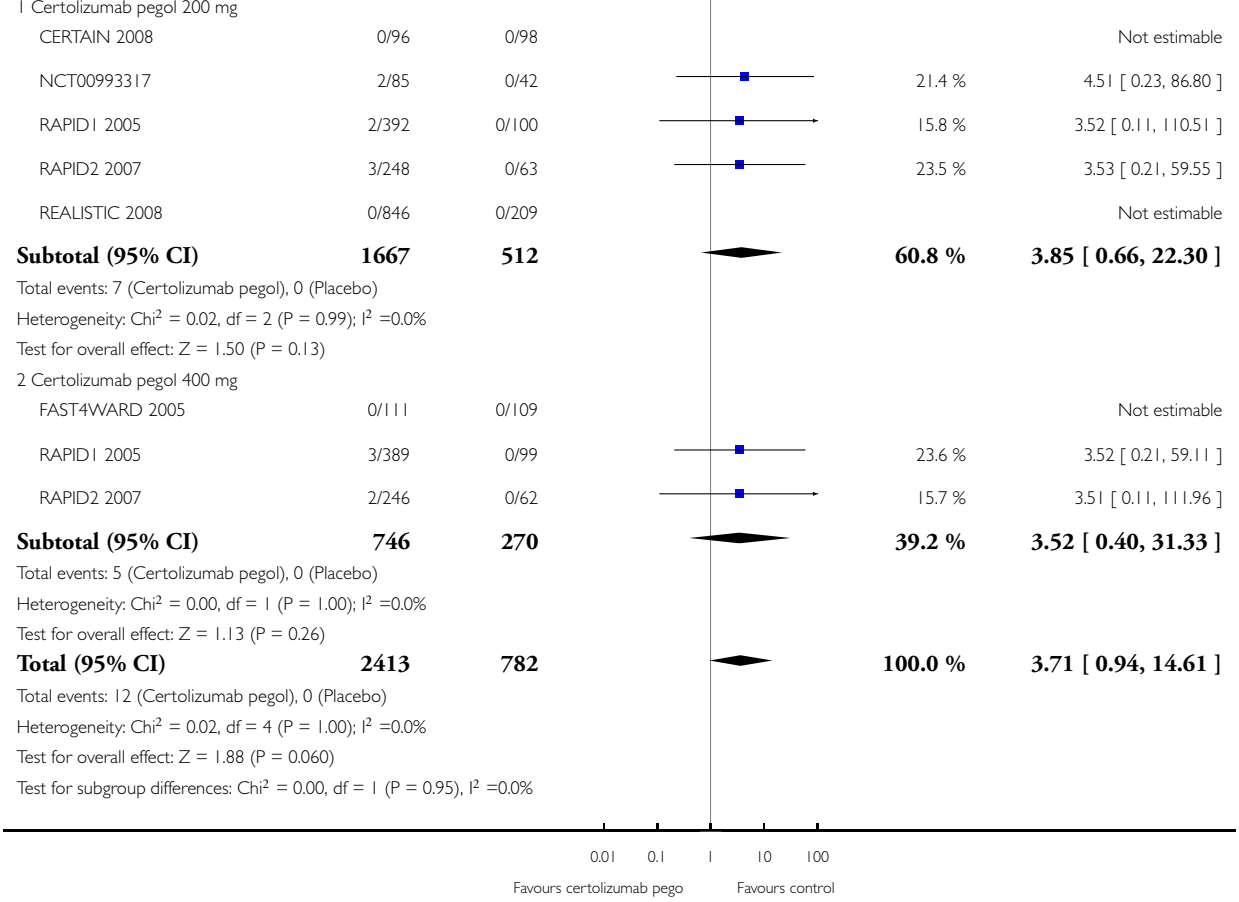
Analysis 49.9. Comparison 49 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 9 Tuberculosis.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 49 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX)

Outcome: 9 Tuberculosis

Study or subgroup	Certolizumab pegol n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Certolizumab pegol 200 mg					
CERTAIN 2008	0/96	0/98			Not estimable
NCT00993317	2/85	0/42		21.4 %	4.51 [0.23, 86.80]
RAPID1 2005	2/392	0/100		15.8 %	3.52 [0.11, 110.51]
RAPID2 2007	3/248	0/63		23.5 %	3.53 [0.21, 59.55]
REALISTIC 2008	0/846	0/209			Not estimable
Subtotal (95% CI)	**1667**	**512**		**60.8 %**	**3.85 [0.66, 22.30]**
Total events: 7 (Certolizumab pegol), 0 (Placebo)					
Heterogeneity: Chi^2 = 0.02, df = 2 (P = 0.99); I^2 =0.0%					
Test for overall effect: Z = 1.50 (P = 0.13)					
2 Certolizumab pegol 400 mg					
FAST4WARD 2005	0/111	0/109			Not estimable
RAPID1 2005	3/389	0/99		23.6 %	3.52 [0.21, 59.11]
RAPID2 2007	2/246	0/62		15.7 %	3.51 [0.11, 111.96]
Subtotal (95% CI)	**746**	**270**		**39.2 %**	**3.52 [0.40, 31.33]**
Total events: 5 (Certolizumab pegol), 0 (Placebo)					
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 1.13 (P = 0.26)					
Total (95% CI)	**2413**	**782**		**100.0 %**	**3.71 [0.94, 14.61]**
Total events: 12 (Certolizumab pegol), 0 (Placebo)					
Heterogeneity: Chi^2 = 0.02, df = 4 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 1.88 (P = 0.060)					
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.95), I^2 =0.0%					

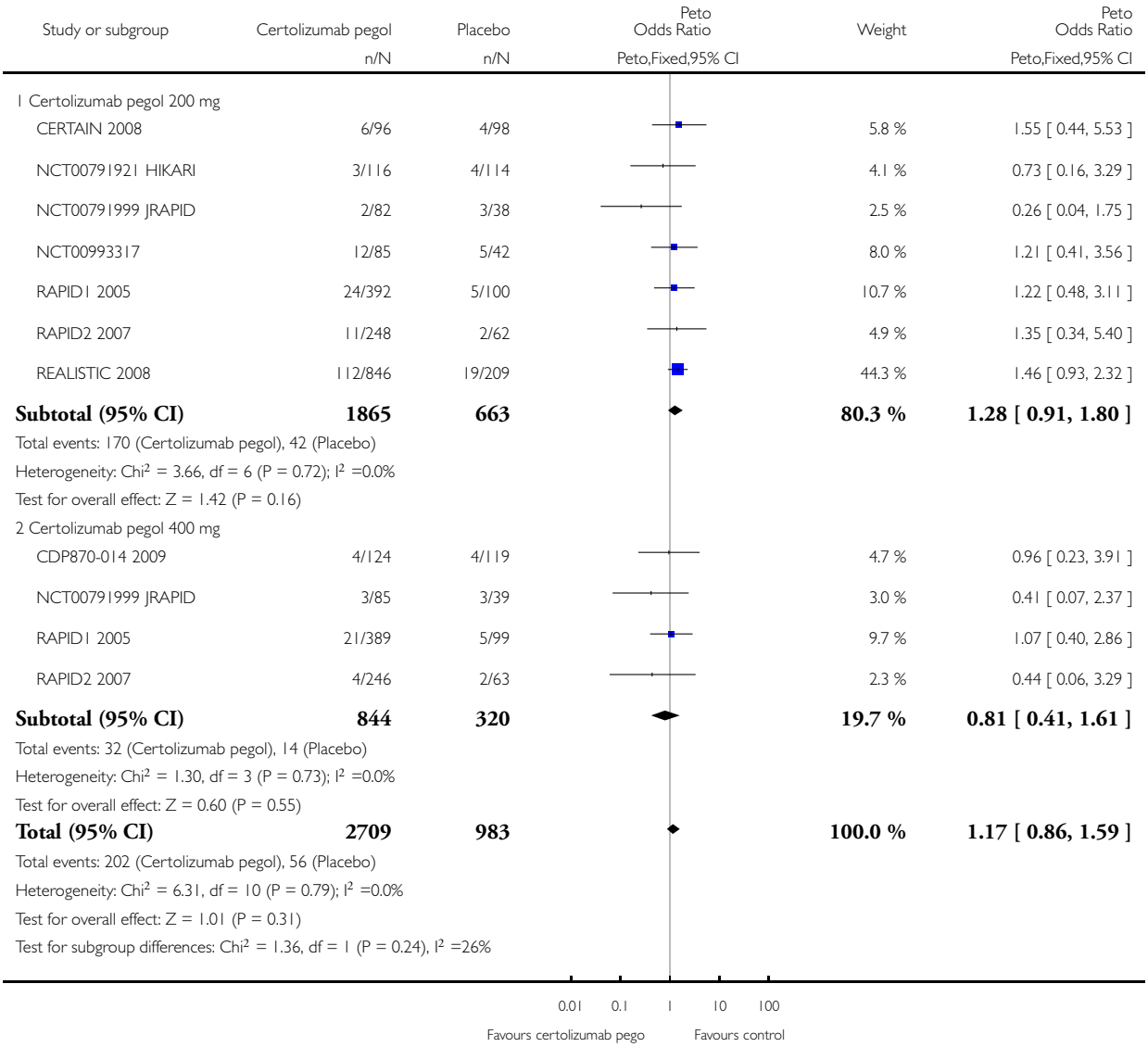


Analysis 49.10. Comparison 49 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 10 Upper respiratory tract infections.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 49 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX)

Outcome: 10 Upper respiratory tract infections

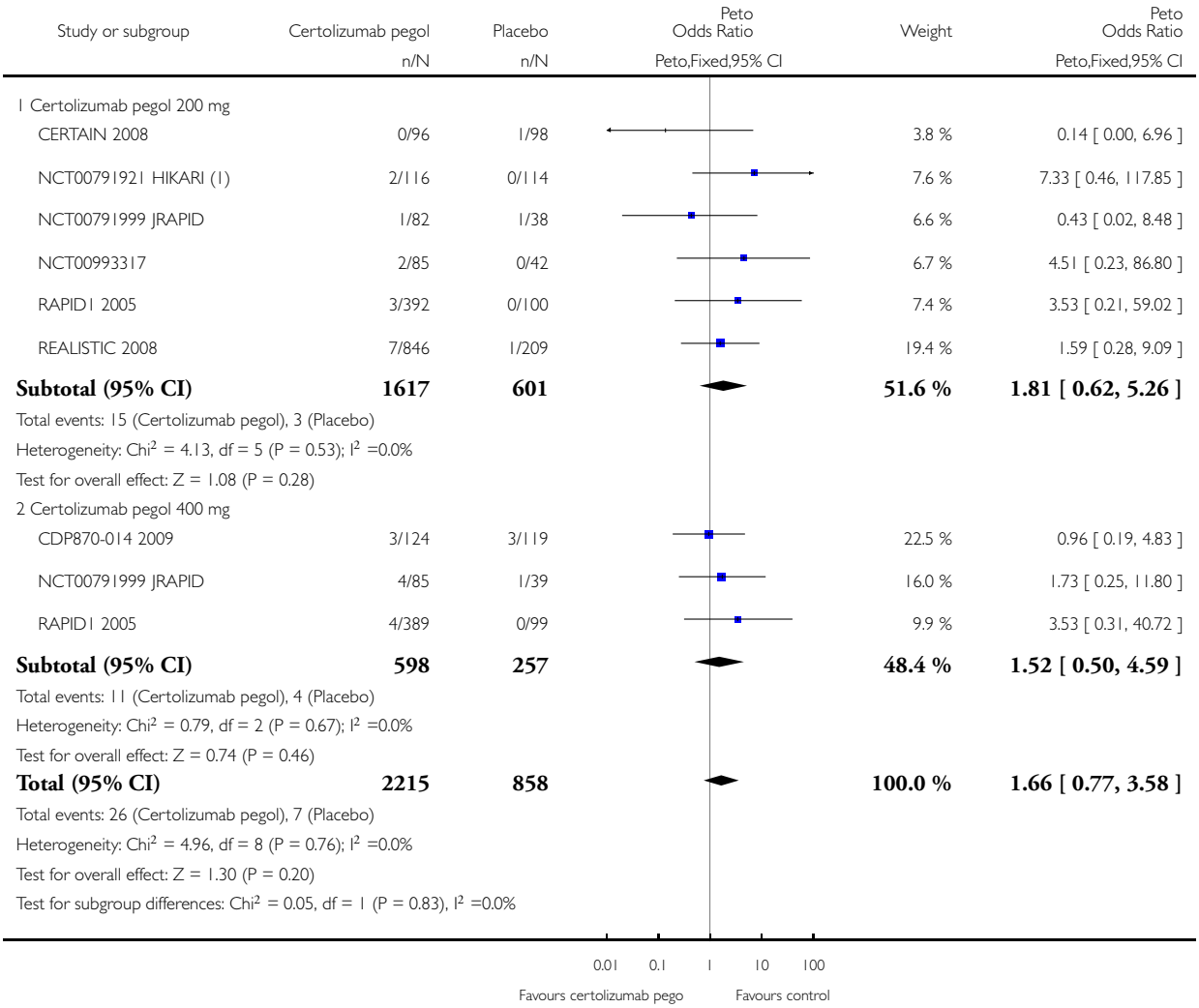


Analysis 49.11. Comparison 49 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 11 Lower respiratory tract infections.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 49 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX)

Outcome: 11 Lower respiratory tract infections



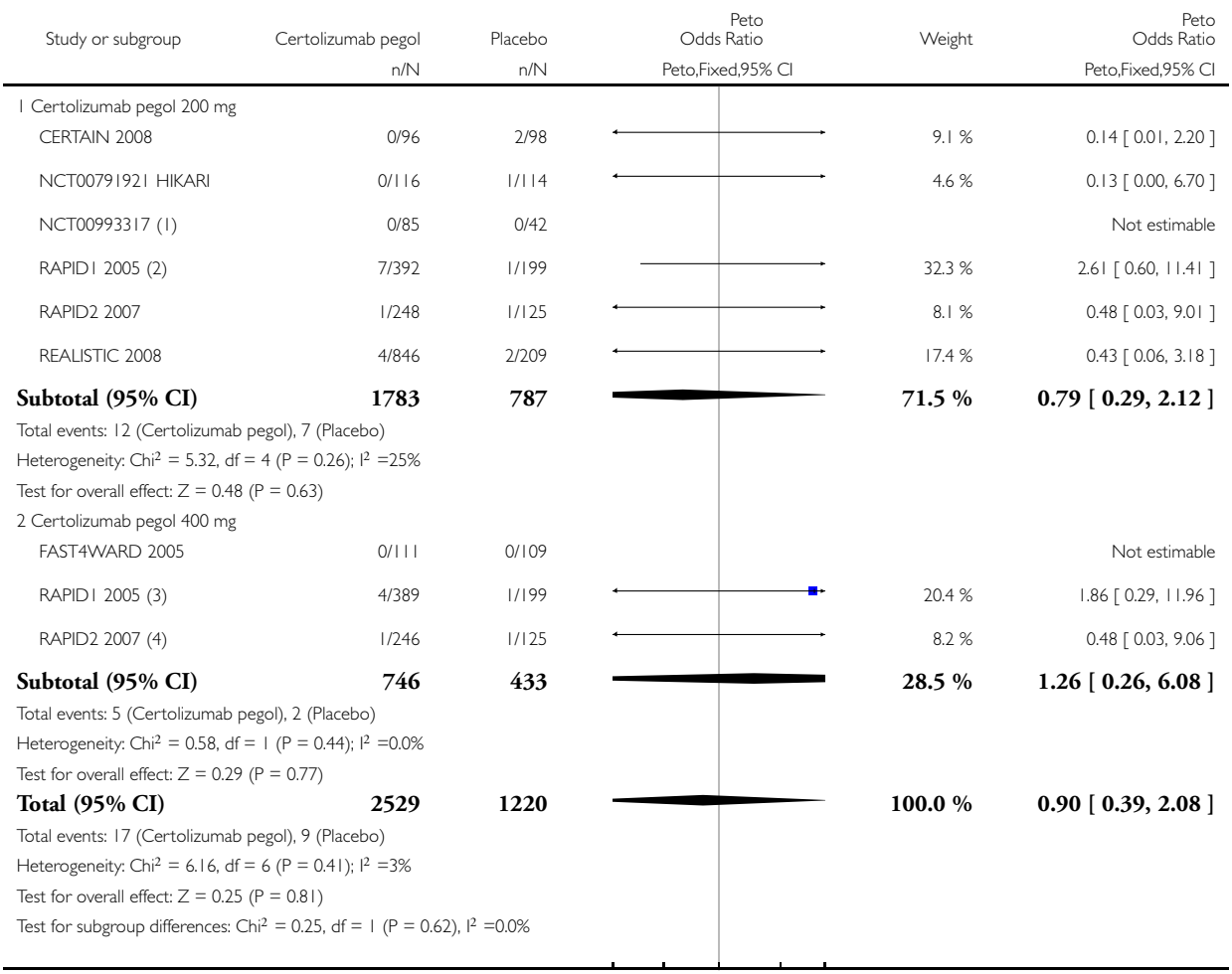
(1) 2(1 pneumonia neumococcal and 1 pneumocystis jirobenzi pneumonia)

Analysis 49.12. Comparison 49 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 12 Malignancies including lymphoma.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 49 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX)

Outcome: 12 Malignancies including lymphoma



system], one adrenal adenoma, one hepatic neoplasm one esophageal carcinoma, and uterine cancer one papilloma.

(1) Data provided by UCB

(2) One patient in the arm of placebo suffered a thyroid neoplasm and 7 in the arm of certolizumab 200 mg sc suffered: three basal cell carcinomas [one with metastasis to the central nervous

(3) In the placebo arm one patient suffered a thyroid neoplasm and 4 in the certolizumab 400 mg sc suffered two tongue neoplasm, 1 extranodal marginal zone B cell limphoma and

(4) One case of malignant neoplasm was reported in each arm, namely bladder cancer in the placebo group and colon cancer in certolizumab pegol 400 mg group

Analysis 50.1. Comparison 50 Analysis of sensibility ACR50, Outcome 1 Doses.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 50 Analysis of sensibility ACR50

Outcome: 1 Doses

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 certolizumab 100 mg sc					
NCT00791999 JRAPID	32/72	4/26		4.3 %	2.89 [1.13, 7.38]
Subtotal (95% CI)	**72**	**26**		**4.3 %**	**2.89 [1.13, 7.38]**
Total events: 32 (Certolizumab pegol), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.22 (P = 0.027)					
2 certolizumab 200 mg sc					
CERTAIN 2008	20/96	7/98		5.7 %	2.92 [1.29, 6.58]
NCT00791999 JRAPID	45/82	4/26		4.5 %	3.57 [1.42, 8.97]
NCT00993317	35/85	8/42		8.4 %	2.16 [1.10, 4.24]
RAPID1 2005	144/393	15/100		16.2 %	2.44 [1.50, 3.96]
RAPID2 2007	80/246	4/64		4.1 %	5.20 [1.98, 13.67]
REALISTIC 2008	226/851	21/212		21.4 %	2.68 [1.76, 4.08]
Subtotal (95% CI)	**1753**	**542**		**60.1 %**	**2.73 [2.13, 3.51]**
Total events: 550 (Certolizumab pegol), 59 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.79, df = 5 (P = 0.73); I^2 =0.0%					
Test for overall effect: Z = 7.85 (P < 0.00001)					
3 certolizumab 400 mg sc					
CDP870-014 2009	22/126	7/121		5.7 %	3.02 [1.34, 6.81]
FAST4WARD 2005	25/111	4/109		3.6 %	6.14 [2.21, 17.05]
NCT00791999 JRAPID	46/85	5/25		5.8 %	2.71 [1.21, 6.07]
RAPID1 2005	155/390	15/99		16.3 %	2.62 [1.62, 4.25]
RAPID2 2007	81/246	4/63		4.1 %	5.19 [1.98, 13.61]
Subtotal (95% CI)	**958**	**417**		**35.6 %**	**3.18 [2.29, 4.41]**
Total events: 329 (Certolizumab pegol), 35 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.42, df = 4 (P = 0.49); I^2 =0.0%					

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 6.94 (P < 0.00001)					
Total (95% CI)	**2783**	**985**	♦	**100.0 %**	**2.89 [2.38, 3.51]**
Total events: 911 (Certolizumab pegol), 98 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 6.73, df = 11 (P = 0.82); I^2 =0.0%					
Test for overall effect: Z = 10.69 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.52, df = 2 (P = 0.77), I^2 =0.0%					

Analysis 50.2. Comparison 50 Analysis of sensibility ACR50, Outcome 2 Size.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 50 Analysis of sensibility ACR50

Outcome: 2 Size

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 certolizumab < 200 patients					
CERTAIN 2008	20/96	7/98		5.7 %	2.92 [1.29, 6.58]
NCT00993317	35/85	8/42		8.4 %	2.16 [1.10, 4.24]
Subtotal (95% CI)	**181**	**140**	◆	**14.1 %**	**2.44 [1.45, 4.10]**
Total events: 55 (Certolizumab pegol), 15 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.31, df = 1 (P = 0.58); I^2 =0.0%					
Test for overall effect: Z = 3.37 (P = 0.00074)					
2 certolizumab > 200 patients					
CDP870-014 2009	22/126	7/121		5.7 %	3.02 [1.34, 6.81]
FAST4WARD 2005	25/111	4/109		3.6 %	6.14 [2.21, 17.05]
NCT00791999 JRAPID	32/72	4/26		4.3 %	2.89 [1.13, 7.38]
NCT00791999 JRAPID	46/85	5/25		5.8 %	2.71 [1.21, 6.07]
NCT00791999 JRAPID	45/82	4/26		4.5 %	3.57 [1.42, 8.97]

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
RAPID1 2005	144/393	15/100		16.2 %	2.44 [1.50, 3.96]
RAPID1 2005	155/390	15/99		16.3 %	2.62 [1.62, 4.25]
RAPID2 2007	80/246	4/64		4.1 %	5.20 [1.98, 13.67]
RAPID2 2007	81/246	4/63		4.1 %	5.19 [1.98, 13.61]
REALISTIC 2008	226/851	21/212		21.4 %	2.68 [1.76, 4.08]
Subtotal (95% CI)	**2602**	**845**		**85.9 %**	**2.97 [2.41, 3.67]**
Total events: 856 (Certolizumab pegol), 83 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.91$, df = 9 (P = 0.75); $I^2 = 0.0\%$					
Test for overall effect: Z = 10.16 (P < 0.00001)					
Total (95% CI)	**2783**	**985**		**100.0 %**	**2.89 [2.38, 3.51]**
Total events: 911 (Certolizumab pegol), 98 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.73$, df = 11 (P = 0.82); $I^2 = 0.0\%$					
Test for overall effect: Z = 10.69 (P < 0.00001)					
Test for subgroup differences: $Chi^2 = 0.47$, df = 1 (P = 0.49), $I^2 = 0.0\%$					

Analysis 50.3. Comparison 50 Analysis of sensibility ACR50, Outcome 3 Use of MTX.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 50 Analysis of sensibility ACR50

Outcome: 3 Use of MTX

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 With MTX					
CDP870-014 2009	22/126	7/121		5.7 %	3.02 [1.34, 6.81]
NCT00993317	35/85	8/42		8.4 %	2.16 [1.10, 4.24]
RAPID1 2005	144/393	15/100		16.2 %	2.44 [1.50, 3.96]
RAPID1 2005	155/390	15/99		16.3 %	2.62 [1.62, 4.25]
RAPID2 2007	81/246	4/63		4.1 %	5.19 [1.98, 13.61]
RAPID2 2007	80/246	4/64		4.1 %	5.20 [1.98, 13.67]
REALISTIC 2008	226/851	21/212		21.4 %	2.68 [1.76, 4.08]
Subtotal (95% CI)	**2337**	**701**		**76.1 %**	**2.77 [2.21, 3.46]**
Total events: 743 (Certolizumab pegol), 74 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.27$, df = 6 (P = 0.64); $I^2 = 0.0\%$					
Test for overall effect: Z = 8.94 (P < 0.00001)					
2 Without MTX					
CERTAIN 2008	20/96	7/98		5.7 %	2.92 [1.29, 6.58]
FAST4WARD 2005	25/111	4/109		3.6 %	6.14 [2.21, 17.05]
NCT00791999 JRAPID	32/72	4/26		4.3 %	2.89 [1.13, 7.38]
NCT00791999 JRAPID	46/85	5/25		5.8 %	2.71 [1.21, 6.07]
NCT00791999 JRAPID	45/82	4/26		4.5 %	3.57 [1.42, 8.97]
Subtotal (95% CI)	**446**	**284**		**23.9 %**	**3.32 [2.23, 4.95]**
Total events: 168 (Certolizumab pegol), 24 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.86$, df = 4 (P = 0.76); $I^2 = 0.0\%$					
Test for overall effect: Z = 5.91 (P < 0.00001)					
Total (95% CI)	**2783**	**985**		**100.0 %**	**2.89 [2.38, 3.51]**
Total events: 911 (Certolizumab pegol), 98 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.73$, df = 11 (P = 0.82); $I^2 = 0.0\%$					
Test for overall effect: Z = 10.69 (P < 0.00001)					
Test for subgroup differences: $Chi^2 = 0.62$, df = 1 (P = 0.43), $I^2 = 0.0\%$					

Analysis 50.4. Comparison 50 Analysis of sensibility ACR50, Outcome 4 Population.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 50 Analysis of sensibility ACR50

Outcome: 4 Population

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Asian trials					
NCT00791999 JRAPID	46/85	5/25		5.8 %	2.71 [1.21, 6.07]
NCT00791999 JRAPID	45/82	4/26		4.5 %	3.57 [1.42, 8.97]
NCT00791999 JRAPID	32/72	4/26		4.3 %	2.89 [1.13, 7.38]
NCT00993317	35/85	8/42		8.4 %	2.16 [1.10, 4.24]
Subtotal (95% CI)	**324**	**119**		**22.9 %**	**2.66 [1.77, 4.00]**
Total events: 158 (Certolizumab pegol), 21 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.80$, df = 3 (P = 0.85); $I^2 = 0.0\%$					
Test for overall effect: Z = 4.72 (P < 0.00001)					
2 Other trials					
CDP870-014 2009	22/126	7/121		5.7 %	3.02 [1.34, 6.81]
CERTAIN 2008	20/96	7/98		5.7 %	2.92 [1.29, 6.58]
FAST4WARD 2005	25/111	4/109		3.6 %	6.14 [2.21, 17.05]
RAPID1 2005	155/390	15/99		16.3 %	2.62 [1.62, 4.25]
RAPID1 2005	144/393	15/100		16.2 %	2.44 [1.50, 3.96]
RAPID2 2007	80/246	4/64		4.1 %	5.20 [1.98, 13.67]
RAPID2 2007	81/246	4/63		4.1 %	5.19 [1.98, 13.61]
REALISTIC 2008	226/851	21/212		21.4 %	2.68 [1.76, 4.08]
Subtotal (95% CI)	**2459**	**866**		**77.1 %**	**2.96 [2.37, 3.70]**
Total events: 753 (Certolizumab pegol), 77 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.71$, df = 7 (P = 0.57); $I^2 = 0.0\%$					
Test for overall effect: Z = 9.60 (P < 0.00001)					
Total (95% CI)	**2783**	**985**		**100.0 %**	**2.89 [2.38, 3.51]**
Total events: 911 (Certolizumab pegol), 98 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.73$, df = 11 (P = 0.82); $I^2 = 0.0\%$					
Test for overall effect: Z = 10.69 (P < 0.00001)					
Test for subgroup differences: $Chi^2 = 0.20$, df = 1 (P = 0.65), $I^2 = 0.0\%$					

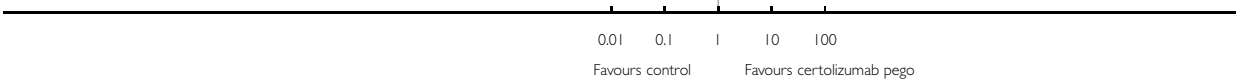
Analysis 50.5. Comparison 50 Analysis of sensibility ACR50, Outcome 5 Duration of previous disease.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 50 Analysis of sensibility ACR50

Outcome: 5 Duration of previous disease

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Long previous disease duration (9 years or more)					
CDP870-014 2009	22/126	7/121		7.2 %	3.02 [1.34, 6.81]
FAST4WARD 2005	25/111	4/109		4.6 %	6.14 [2.21, 17.05]
Subtotal (95% CI)	**237**	**230**		**11.7 %**	**4.02 [2.02, 7.98]**
Total events: 47 (Certolizumab pegol), 11 (Control)					
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 1.15$, df = 1 (P = 0.28); $I^2 = 13\%$					
Test for overall effect: Z = 3.97 (P = 0.000073)					
2 Short previous disease duration (less than 7 years)					
NCT00993317	35/85	8/42		10.5 %	2.16 [1.10, 4.24]
RAPID1 2005	144/393	15/100		20.3 %	2.44 [1.50, 3.96]
RAPID1 2005	155/390	15/99		20.5 %	2.62 [1.62, 4.25]
RAPID2 2007	81/246	4/63		5.1 %	5.19 [1.98, 13.61]
RAPID2 2007	80/246	4/64		5.1 %	5.20 [1.98, 13.67]
REALISTIC 2008	226/851	21/212		26.8 %	2.68 [1.76, 4.08]
Subtotal (95% CI)	**2211**	**580**		**88.3 %**	**2.75 [2.18, 3.47]**
Total events: 721 (Certolizumab pegol), 67 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.23$, df = 5 (P = 0.52); $I^2 = 0.0\%$					
Test for overall effect: Z = 8.53 (P < 0.00001)					
Total (95% CI)	**2448**	**810**		**100.0 %**	**2.87 [2.31, 3.57]**
Total events: 768 (Certolizumab pegol), 78 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.52$, df = 7 (P = 0.48); $I^2 = 0.0\%$					
Test for overall effect: Z = 9.47 (P < 0.00001)					
Test for subgroup differences: $Chi^2 = 1.05$, df = 1 (P = 0.30), $I^2 = 5\%$					



Analysis 50.6. Comparison 50 Analysis of sensibility ACR50, Outcome 6 Published vs unpublished studies.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 50 Analysis of sensibility ACR50

Outcome: 6 Published vs unpublished studies

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Published studies					
CDP870-014 2009	22/126	7/121		5.7 %	3.02 [1.34, 6.81]
FAST4WARD 2005	25/111	4/109		3.6 %	6.14 [2.21, 17.05]
RAPID1 2005	144/393	15/100		16.2 %	2.44 [1.50, 3.96]
RAPID1 2005	155/390	15/99		16.3 %	2.62 [1.62, 4.25]
RAPID2 2007	81/246	4/63		4.1 %	5.19 [1.98, 13.61]
RAPID2 2007	80/246	4/64		4.1 %	5.20 [1.98, 13.67]
REALISTIC 2008	226/851	21/212		21.4 %	2.68 [1.76, 4.08]
Subtotal (95% CI)	**2363**	**768**		**71.3 %**	**2.97 [2.36, 3.73]**
Total events: 733 (Certolizumab pegol), 70 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.71$, df = 6 (P = 0.46); $I^2 = 0.0\%$					
Test for overall effect: Z = 9.25 (P < 0.00001)					
2 Unpublished studies					
CERTAIN 2008	20/96	7/98		5.7 %	2.92 [1.29, 6.58]
NCT00791999 JRAPID	45/82	4/26		4.5 %	3.57 [1.42, 8.97]
NCT00791999 JRAPID	46/85	5/25		5.8 %	2.71 [1.21, 6.07]
NCT00791999 JRAPID	32/72	4/26		4.3 %	2.89 [1.13, 7.38]
NCT00993317	35/85	8/42		8.4 %	2.16 [1.10, 4.24]
Subtotal (95% CI)	**420**	**217**		**28.7 %**	**2.71 [1.89, 3.90]**
Total events: 178 (Certolizumab pegol), 28 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.83$, df = 4 (P = 0.93); $I^2 = 0.0\%$					
Test for overall effect: Z = 5.38 (P < 0.00001)					
Total (95% CI)	**2783**	**985**		**100.0 %**	**2.89 [2.38, 3.51]**
Total events: 911 (Certolizumab pegol), 98 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.73$, df = 11 (P = 0.82); $I^2 = 0.0\%$					
Test for overall effect: Z = 10.69 (P < 0.00001)					
Test for subgroup differences: $Chi^2 = 0.17$, df = 1 (P = 0.68), $I^2 = 0.0\%$					

ADDITIONAL TABLES

Table 1. Demographic and disease characteristics of the retrieved phase III trials

Study	FAST4WAR n = 220	CDP870-014 n = 247	RAPID1 n = 982	RAPID2 n = 619	CT0099331 n = 127	CERTAIN n = 194	REALISTIC n = 1063	HIKARI n =230	JRAPID n = 316
Age (years) Mean ± (SD)	53.8 (12.2) CZP 400mg 52.7 (12.7) Placebo 54.0 (11.6)	CZP 400mg plus MTX 53 (12.0) Placebo plus MTX 55.6 (11.7)	52.0 (11.6) CZP 200mg plus MTX 51.4 (11.6) CZP 400 mg plus MTX 52.4 (11.7) Placebo plus MTX 52.2 (11.2)	51.9 (11.5) CZP 200mg plus MTX 52.2 (11.1) CZP 400 mg plus MTX 51.9 (11.8) Placebo plus MTX 51.5 (11.8)	CZP 200mg plus MTX 18-65 years= 72; > 65 years =13 Placebo plus MTX 18-65 years= 38; > 65 years =4	CZP 200mg 53.6 (11.9) Placebo 54.0(12.4)	55.1 (12.49) CZP 200mg 55.4 (12.4) Placebo 53.9 (12.7)	55.7 (10.0) CZP 200mg 56.0 (10.2) Placebo 55.4 (9.8)	53.0 (11.0) CZP 100mg 54.3 (10.6) CZP 200mg 50.6 (11.4) CZP 400 mg 55.4 (10.3) Placebo 51.9 (11.1)
Follow up	24 weeks	24 weeks	52 weeks	24 weeks	24 weeks	24 weeks	12 weeks	12 and 24 weeks	12 and 24 weeks
Female n (%)	184 (83.6%)	CZP 400mg plus MTX 72% Placebo plus MTX 66.1 %	817 (83.2%) CZP 200mg 324 (82.4%) CZP 400 mg 326 (83.6%) Placebo 167 (83.9%)	505 (81.6%) CZP 200mg 206 (83.7%) CZP 400 mg 192 (78%) Placebo 107 (84.3%)	112 (88.2%) CZP 200mg 75 (59.1%) Placebo 37 (29.13%)	156 (80.4%) CZP 200mg 81 (41.8%) Placebo 75 (38.7%)	829 (78%) CZP 200mg 660 (62.1%) Placebo 169 (15.9%)	171 (74.3%) CZP 200mg 83 (36.1%) Placebo 88 (38.3 %)	CZP 100mg 58 (18.4%) CZP 200mg 69 (21.8%) CZP 400 mg 69 (21.8%) Placebo 66 (20.9 %)
Disease duration (years) Mean (SD)	9.5 (NC) CZP 400mg 8.7 (8.2) Placebo 10.4 (9.6)	CZP plus MTX 9.4 (7.5) Placebo plus MTX 9.9 (7.8)	6.1 (4.3) CZP 200mg 6.1 (4.2) CZP 400 mg 6.2 (4.4) Placebo 6.2 (4.4)	6.2 (4.2) CZP 200mg 6.1 (4.1) CZP 400 mg 6.5 (4.3) Placebo 5.6 (3.9)	CZP 200mg 6.4 (4.2) Placebo 6 (5.1)		6.2 (4.2) CZP 200mg 8.6 (8.8) Placebo 8.9 (9.1)		

Table 1. Demographic and disease characteristics of the retrieved phase III trials (*Continued*)

RF positive (³ 14 IU/ml) (%)	100% CZP 400mg 110 (99.9%) Placebo 109 (100%)	78%	81.8% CZP 200mg 312 (79.6%) CZP 400 mg 326 (83.6%) Placebo 164 (82.8%)	76.9% CZP 200mg 186 (77.5%) CZP 400 mg 179 (75.5%) Placebo 97 (78.2%)			CZP 200mg 555 (73.9%) Placebo 137 (78.2%)		
MTX concomitant dose (mg/week) Mean (SD)	N/A	CZP plus MTX 16.9 (3.9) Placebo plus MTX 16.6 (3.6)	13.6 CZP 200mg 13.6 (4.3) CZP 400 mg 13.6 (4) Placebo 13.4 (4.2)	12.5 CZP 200mg 12.5 (3.6) CZP 400 mg 12.6 (3.7) Placebo 12.2 (3.3)	CZP 200mg 13.4 (2.5) Placebo 13.6 (2.8)	N/A	CZP 200mg 17.2 (5.7) Placebo 16.3 (5.3)	N/A	N/A
Number of previous DMARDS Mean (SD)	2.0 CZP 400mg 2.0 (1.2) Placebo 2.0 (1.3)	1.3	1.3 CZP 200mg 1.3 (1.3) CZP 400 mg 1.3 (1.3) Placebo 1.4 (1.4)	1.2 CZP 200mg 1.2 (1.3) CZP 400 mg 1.3 (1.2) Placebo 1.2 (1.2)	1.2 CZP 200mg 3.3 (1.3) Placebo 3.2 (1.5)				
Tender Joint count Mean (0-66) (SD)	29.0 (13.13)	CZP plus MTX 29 (11.6) Placebo plus MTX 31 (12.9)	30.7 (12.9)	30.2 (14.0)	CZP 200mg 25.04 (14.94) Placebo 25.05 (14.61)		CZP 200mg 14.7 (6.6) Placebo 14.7 (6.6)		
Swollen Joint Count Mean (0-66) (SD)	20.5 (9.67)	CZP plus MTX 22.8 (9.4) Placebo plus MTX 22.2 (9.6)	21.5 (9.8)	21.0 (9.8)	CZP 200mg 15.96 (8.86) Placebo 17.31 (11.18)		CZP 200mg 11.8 (5.6) Placebo 11.1 (5.2)		
HAQ-DI mean (SD)	1.5 (0.64)	CZP plus MTX 1.4 (0.6)	1.7 (0.60)	1.6 (0.59)	CZP 200mg 1.		CZP 200mg 1.5		

Table 1. Demographic and disease characteristics of the retrieved phase III trials (*Continued*)

		Placebo plus MTX 1.5 (0.7)			43 (0.67) Placebo 1. 53 (0.74)		(0.6) Placebo 1. 6 (0.6)		
CRP (mg/ L) Geo- metric mean (CV)	11.5 (NC)	CZP plus MTX 11.9 Placebo plus MTX 13.1	14.7 (144. 2)	13.6 (180. 9)			CZP 200mg 9 Placebo 10		
DAS- 28 (ESR) Mean (SD)	6.3 (1.00)	6.2 (0.99)	6.9 (0.8)	6.8 (0.83)			CZP 200mg 6.4 (0.9) Placebo 6. 4 (0.9)		

Notes: CZP = certolizumab pegol; CV = coefficient of variation; DAS = disease activity score; DMARD = disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; IU = international units; L = litre; mg = milligrams; mL = millilitres; RF= rheumatoid factor; SD = standard deviation; Y = years; NC = not calculated; N/A = not applicable. All randomised subjects; the actual numbers vary slightly across parameters

Notes: CZP = ce gol; CV = coef ation; DAS = score; DMARD fying antirheuma erythrocyte sedi IU = internatio litre; mg = mil millilitres; RF= r tor; SD = stand Y = years; NC lated; N/A = not randomised subj numbers vary sli rameters

Table 2. Flow of patients in the phase III trials retrieved

Study	Placebo	Certolizumab pegol 100 mg	Certolizumab pegol 200 mg	Certolizumab pegol 400 mg
RAPID1 n = 982	ITT n = 199 Safety n = 199		ITT n = 393 Safety [a] n = 392	ITT n = 390 Safety n = 389
	Withdrawn at week 16 due to lack of efficacy n = 125 (62.8%)		Withdrawn at week 16 due to lack of efficacy n = 83 (21.1%)	Withdrawn at week 16 due to lack of efficacy n = 68 (17.4%)
	All withdrawn n = 156 (78.4%)		All withdrawn n = 138 (35.1)	All withdrawn n = 116 (39.7%)

Table 2. Flow of patients in the phase III trials retrieved (*Continued*)

	Completed n = 43 (21.6%)		Completed n = 255 (64.9%)	Completed n = 274 (70.3%)
RAPID2 **n = 619**	ITT n = 127[c] Safety n = 125		ITT n = 246 Safety n = 248	ITT n = 246 Safety n = 246
	Withdrawn at week 16 due to lack of efficacy n = 103 (81%)		Withdrawn at week 16 due to lack of efficacy n = 52 (21.1%)	Withdrawn at week 16 due to lack of efficacy n = 52 (21.1%)
	All withdrawn n = 110 (86%)		All withdrawn n = 72 (29.3%)	All withdrawn n = 65 (26.4%)
	Completed n = 17 (13.4%)		Completed n = 174 (70.7%)	Completed n = 181 (73.6%)
FAST4WARD	ITT n = 109 Safety n = 109			ITT n = 111 Safety n = 111
	All withdrawn n = 81 (74%) 75 (68.8%) Lack of efficacy 2 (1.8%) Adverse event 1 (0.9%) Protocol violation 3 (2.8) Lost to follow-up			All withdrawn n = 35 (31.5%) 24 (21.6%) Lack of efficacy 5 (4.5%) Adverse event 4 (3.6%) Protocol violation 2 (1.8%) Consent withdrawn
	Completed n = 28 (25.7%)			Completed n = 76 (68.5%)
CDP870-014	ITT n = 121[d] Safety n = 119			ITT n = 126[d] Safety n = 124
	All withdrawn n = 56 (46.3%) 45 (37.2%) Lack of efficacy 6 (5%) Adverse event 5 (4.1%) Other reasons			All withdrawn n = 28 (22.2%) 16 (12.7%) Lack of efficacy 7 (5.6%) Adverse event 5 (4%) Other reasons
	Completed n = 65 (53.7%)			Completed n = 98 (77.8%)

Table 2. Flow of patients in the phase III trials retrieved (*Continued*)

NCT00993317	ITT n =42 Safety n = 42		ITT n = 85 Safety n = 85	
	All withdrawn n = 21 (50%) 18 (42%) Lack of efficacy 2 (4.76%) Adverse event 1 (2.38%) Other reasons		All withdrawn n = 25 (29.41%) 18 (21.8%) Lack of efficacy 4 (4.70%) Adverse event 3 (3.52%) Other reasons	
	Completed n = 21 (50%)		Completed n = 60 (70.58%)	
CERTAIN	ITT n = 98 Safety n = 98		ITT n = 96 Safety n = 96	
	All withdrawn n = 18 (18.36%) 7 (7.14%) Lack of efficacy 6 (6.12 %) Adverse event 5 (5.10%) Other reasons		All withdrawn n = 12 (12.5%) 2 (2.08 %) Lack of efficacy 6 (6.25%) Adverse event 4 (4.16%) Other reasons	
	Completed n = 80 (81.63%)		Completed n = 84 (87.5%)	
REALISTIC	ITT n = 212 Safety n =		ITT n = 851 Safety n =	
	All withdrawn n = 28 (13.20%) 6 (2.83%) Lack of efficacy 6 (2.83%) Adverse event 16 (7.54%) Other reasons		All withdrawn n = 80 (9.41%) 6 (0.70%) Lack of efficacy 33 (3.87%) Adverse event 41 (4.81%) Other reasons	
	Completed n = 184 (86.79%)		Completed n = 771 (90.59%)	
HIKARI	ITT n = 114 Safety n = 114		ITT n = 116 Safety n = 116	
	All withdrawn n = 96 (84.2%) 2 (1.75%) Lack of efficacy 2 (1.75%) Adverse event 94 (82%) Other reasons (protocol planned n =88)		All withdrawn n = 34 (29.31%) 0 (0%) Lack of efficacy 8 (6.9%) Adverse event 26 (22.4%) Other reasons (protocol planned n =24)	

Table 2. Flow of patients in the phase III trials retrieved (*Continued*)

	Completed n = 18 (15.8%)		Completed n = 82 (70.69%)	
JRAPID	ITT n = 77 Safety n = 77	ITT n = 72 Safety n = 72	ITT n = 82 Safety n = 82	ITT n = 85 Safety n = 85
	All withdrawn n = 52 (67.53%) 2 (2.98%) Lack of efficacy 3 (3.90%) Adverse event 47 (61.04%) Other reasons (Protocol planned withdrawal 45)	All withdrawn n = 21 (29.17%) 3 (4.17%) Lack of efficacy 0 (0%) Adverse event 18 (25%) Other reasons (Protocol planned withdrawal 14)	All withdrawn n = 16 (19.51%) 1 (1.22%) Lack of efficacy 3 (3.66%) Adverse event 12 (14.63%) Other reasons (Protocol planned withdrawal 11)	All withdrawn n = 20 (23.53%) 0 (0%) Lack of efficacy 7 (8.23%) Adverse event 13 (15.29%) Other reasons (Protocol planned withdrawal 11)
	Completed n = 25 (32.47%)	Completed n = 51 (70.83%)	Completed n = 66 (80.49%)	Completed n = 65 (76.47%)

a One patient withdrew by her own decision
b One patient was discontinued due to the ESR/CRP not meeting criteria
c Two patients in the placebo group received certolizumab pegol and were included for safety in the 200 mg group
d Two patients in the each of treatment groups did not take study medication. Manufactures reported efficacy calculations from placebo n = 119 and certolizumab pegol n = 124

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Table 3. Beneficial ACR50

	Follow up	Doses/study	Response rate certolizumab pegol	Response rate placebo	RR (IC95%)	% RD	NNT
ACR50							
Analysis 2.2	24 weeks	200 mg/ CERTAIN 2008; NCT00791999 JRAPID; NCT00993317;	36%	9%	3.80 (2.42 to 5. 95)	27 (20 to 33)	4 (3 to 8)

Table 3. Beneficial ACR50 (*Continued*)

		RAPID1 2005; RAPID2 2007					
Analysis 3.2	24 weeks	400 mg/ CDP870-014 2009; FAST4WARD 2005; NCT00791999 JRAPID; RAPID1 2005; RAPID2 2007	34%	7%	4.65 (3.09 to 6.99)	27 (17 to 34)	4 (3 to 7)
Analysis 5.2	52 weeks	200 mg/ RAPID1 2005,	38%	8%	5.03 (3.04 to 8.32)	30 (24 to 36)	4 (2 to 7)
Analysis 6.2	52 weeks	400 mg/ RAPID1 2005	40%	8%	5.27 (3.19 to 8.71)	32 (26 to 38)	3 (2 to 6)

Table 4. Health-related quality of life

	Follow-up	Doses/study	Mean differences
HAQ (0-3) (Best=0; Worst 3)			
Analysis 11.1	24 weeks	200 mg/ CERTAIN 2008; NCT00993317; RAPID1 2005; RAPID2 2007	-0.35 (-0.43 to -0.26)
Analysis 11.2	24 weeks	400 mg/ CDP870-014 2009; FAST4WARD 2005; RAPID1 2005; RAPID2 2007	-0.38 (-0.48 to -0.28)
	52 weeks	200 mg/ RAPID1 2005	-0.42 (-0.54 to -0.30)
	52 weeks	400 mg/ RAPID1 2005	-0.45 (-0.57 to -0.33)
SF-36 PCS (0-100) (Worst=0; Best=100)			
Analysis 14.1	24 weeks	200 mg/ CERTAIN 2008; RAPID1 2005; RAPID2 2007	5.03 (3.90 to 6.16)
Analysis 14.2	24 weeks	400 mg/ CDP870-014 2009; RAPID1 2005; RAPID2 2007	5.54 (4.11 to 6.97)

Table 4. Health-related quality of life (*Continued*)

SF-36 MCS (0-100) (Worst=0; Best=100)			
Analysis 15.1	24 weeks	200 mg/ RAPID1 2005; RAPID2 2007	4.18 (2.70 to 5.66)
Analysis 15.2	24 weeks	400 mg/ CDP870-014 2009; RAPID1 2005; RAPID2 2007	4.05 (2.77 to 5.34)
SF-36 PCS			
Analysis 16.1	52 weeks	200 mg/ RAPID1 2005	6.06 (4.59 to 7.53)
Analysis 16.2	52 weeks	400 mg/ RAPID1 2005	6.88 (5.42 to 8.34)
SF-36 MCS (0-100) (Worst=0; Best=100)			
	52 weeks	200 mg/ RAPID1 2005	4.3 (2.4 to 6.2)
	52 weeks	400 mg/ RAPID1 2005	4.3 (2.4 to 6.2)
Patients VAS score (0-100)			
	24 weeks	200 mg/ RAPID1 2005; RAPID2 2007	-20.48 (-24.26 to -16.69)
		400 mg/ RAPID1 2005; RAPID2 2007; FAST4WARD 2005	-21.35 (-25.08 to -17.61)
	52 weeks	200 mg/ RAPID1 2005	-22.20 (-27.37 to -17.03)
		400 mg/ RAPID1 2005	-24.70 (-29.73 to -19.67)
DAS-28 remission (< 2.6)			
Analysis 25.2	24 weeks	200 mg/CERTAIN 2008; NCT00791921 HIKARI; RAPID1 2005; RAPID2 2007	8.47 (4.15 to 17.28)
Analysis 25.3		400 mg/ CDP870-014 2009; RAPID1 2005; RAPID2 2007	7.18 (3.12 to 16.50)
Analysis 25.4	52 weeks	200 mg/ RAPID1 2005	10.36 (3.29 to 32.58)
Analysis 25.5		400 mg/ RAPID1 2005	12.49 (3.99 to 39.12)

Table 5. Radiological changes

	Follow up	Doses/study	Mean differences
Modified Total Sharp Scores (mTTS) is the sum of the erosion score (ES) and the joint space narrowing (JSN) score and has a range of 0 to 398			
Analysis 44.1	24 weeks	200 mg/ RAPID1 2005; RAPID2 2007	-1.06 (-1.58 to -0.55)
Analysis 44.2	24 weeks	400 mg/ RAPID1 2005; RAPID2 2007	-1.32 (-1.85 to -0.78)
	52 weeks	200 mg/ RAPID1 2005	-2.4 (-4.11 to -0.69)
	52 weeks	400 mg/ RAPID1 2005	-2.6 (-4.29 to -0.91)
Erosion Score is the sum of joint scores collected for 46 joints and has a range of 0 to 230			
Analysis 33.1	24 weeks	200 mg/ RAPID1 2005; RAPID2 2007	-0.67 (-0.96 to -0.38)
Analysis 33.2	24 weeks	400 mg/ RAPID1 2005; RAPID2 2007	-0.76 (-1.14 to -0.37)
	52 weeks	200 mg/ RAPID1 2005	-1.4 (-2.32 to -0.48)
	52 weeks	400 mg/ RAPID1 2005	-1.5 (-2.44 to -0.56)
Joint space narrowing (JSN) is the sum of joint scores collected for 42 joints and has a range of 0 to 168			
Analysis 36.1	24 weeks	200 mg/ RAPID1 2005; RAPID2 2007	-0.45 (-0.77 to -0.13)
Analysis 36.2	24 weeks	400 mg/ RAPID1 2005; RAPID2 2007	-0.55 (- 0.86 to -0.24)
	52 weeks	200 mg/ RAPID1 2005	-1 (-1.85 to -0.15)
	52 weeks	400 mg/ RAPID1 2005	-1.2 (-1.98 to -0.42)

Table 6. Adverse events

	Studies	Response rate in % (number of events) certolizumab pegol	Response rate in % (number of events) placebo	RR	% RD	NNTH
Serious adverse events (doses)				**Peto OR**		
Analysis 8.6 200 mg certolizumab pegol	CERTAIN 2008; NCT00791921 HIKARI; NCT00791999 JRAPID; NCT00993317; RAPID1 2005; RAPID2 2007; REALISTIC 2008	7% (145)	4% (38)	1.77 (1.27 to 2.46)	4 (2 to 6)	35 (19 to 98)
Analysis 9.7 400 mg certolizumab pegol	CDP870-014 2009; FAST4WARD 2005; NCT00791999 JRAPID; RAPID1 2005; RAPID2 2007	10% (95)	4% (31)	1.98 (1.36 to 2.9)	5 (2 to 7)	28 (15 to 74)
Adverse events leading to withdrawal				**Peto OR**		
Analysis 8.9 200 mg certolizumab pegol	CERTAIN 2008; NCT00791921 HIKARI; NCT00791999 JRAPID; NCT00993317; RAPID1 2005; RAPID2 2007; REALISTIC 2008	4% (90)	3% (26)	1.62 (1.07 to 2.44)	2 (0 to 4)	57 (25 to 492)
Analysis 9.9 400 mg certolizumab	CDP870-014 2009; FAST4WARD	5% (48)	2% (16)	2.01 (1.20 to 3.36)	3 (1 to 5)	52 (23 to 257)

Table 6. Adverse events (*Continued*)

pegol	2005; NCT00791999 JRAPID; RAPID1 2005; RAPID2 2007					
Death				**Peto OR**		
Analysis 8.10 200 mg certolizumab pegol	CERTAIN 2008; NCT00791921 HIKARI; RAPID1 2005; RAPID2 2007; REALISTIC 2008	0.3% (6)	0.1% (1)	2.56 (0.56 to 11.6)	0 (-1 to 1)	NS
Analysis 9.10 400 mg certolizumab pegol	CDP870-014 2009; FAST4WARD 2005; RAPID1 2005; RAPID2 2007	0.5% (5)	0% (0)	2.16 (0.40 to 11.79)	0 (-1 to 1)	NS
See analysis 49.8.3 Other doses	Choy 2002; NCT00791999 JRAPID	0.01 (1)	0% (0)	4.48 (0.07 to 286.49)	0.01 (-0.05 to 0.08)	NS
Malignancies (neoplasias including lymphoma) Analysis 49.12				**Peto OR 0.90 (0.39 to 2.08)**		NS
200 mg certolizumab pegol	CERTAIN 2008; NCT00791921 HIKARI; NCT00993317; RAPID1 2005; RAPID2 2007; REALISTIC 2008	0.6% (12)	0.9% (7)	0.79 (0.29 to 2.12)	0 (-1 to 1)	NS
400 mg certolizumab pegol	FAST4WARD 2005; RAPID1 2005; RAPID2 2007	0.6 % (5)	0.4% (2)	1.26 (0.26 to 6.08)	0 (-1 to 1)	NS

Table 6. Adverse events (*Continued*)

Infections and infestations				**RR**		
Analysis 8.33 200 mg certolizumab pegol	CERTAIN 2008; NCT00791921 HIKARI; NCT00791999 JRAPID; NCT00993317; RAPID1 2005; RAPID2 2007; REALISTIC 2008	32% (559)	25% (247)	1.29 (1.07 to 1.56)	7 (1 to 13)	14 (8 to 58)
Analysis 9.40 400 mg certolizumab pegol	CDP870-014 2009; NCT00791999 JRAPID; RAPID1 2005; RAPID2 2007	34% (293)	21% (111)	1.49 (1.11 to 1.99)	10 (1 to 20)	10 (5 to 44)
Tuberculosis				**Peto OR** 3.71 (0.94 to 14.61)	Not calculated	NS
Analysis 49.9	Overall	0.5% (12)	0% (0)	3.71 (0.94 to 14.61)	Not calculated	NS
Analysis 8.11 200 mg certolizumab pegol	CERTAIN 2008; NCT00993317; RAPID1 2005; RAPID2 2007; REALISTIC 2008	0.4% (7)	0% (0)	4.53 (0.94 to 21.85)	Not calculated	NS
Analysis 9.13 400 mg certolizumab pegol	FAST4WARD 2005; RAPID1 2005; RAPID2 2007	0.6% (5)	0% (0)	4.55 (0.71 to 29.11)	Not calculated	NS

APPENDICES

Appendix 1. MEDLINE search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
1 (CDP870 or CDP 870 or "certolizumab pegol" or certolizumab or CDP-870 or cimzia).mp. (393)
2 ("Rheumatoid Arthritis" or (Caplan$ and Syndrome?) or (Felty$ and S?ndrome) or (Rheumatoid and Nodule?) or (Sjogren$ and S?ndrome?) or (Sicca$ and S?ndrome?) or (Ankylos$ and Spondylit$) or (Spondylarthritis and Ankylopoietica) or (Rheumatoid$ and Spondylit$) or (Bechterew$ and Disease?) or (Marie-Struempell and Disease?) or (Adult and Onset and Still$ and Disease?)).mp. (98824)
3 exp Arthritis, Rheumatoid/ (94528)
4 2 or 3 (126632)
5 1 and 4 (131)
6 Clinical trial.pt. (473242)
7 randomized.ab. (256728)
8 Placebo.ab. (140242)
9 dt.fs. (1573096)
10 randomly.ab. (187872)
11 trial.ab. (264547)
12 groups.ab. (1216413)
13 or/6-12 (3112539)
14 5 and 13 (114)
15 limit 14 to yr="2009 -Current" (99)
Search date: 2009-February 12, 2013

Appendix 2. EMBASE search strategy

1. 'rheumatoid arthritis'/exp/
2. 'certolizumab pegol'/exp/
3. (CDP870 OR 'CDP 870' OR CDP-870 OR 'certolizumab pegol' OR certolizumab OR cimzia).mp.
4. 2 OR 3
5. 4 AND 1
6. random:.tw.
7. clinical trial:.mp.
8. exp health care quality
9. or/6-8
10. 5 AND 9
Search date: 2009-February 12, 2013

Appendix 3. CINAHL search strategy

1.'rheumatoid arthritis'/exp/
2."rheumatoid arthritis".mp.
3. (CDP870 OR 'CDP 870' OR CDP-870 OR 'certolizumab pegol' OR certolizumab OR cimzia).mp.
4.(1 or 2) and 3
5.exp prognosis
6.exp study design
7.random:.mp.
8.or/ 5-7
9.4 and 8
Search date: 2009-February 12, 2013

Appendix 4. Search strategy for CDSR and CENTRAL, HTA, DARE, NHS EED

Last search on November 2009
#1 certolizumab or cimzia
#2 cdp870
#3 cdp next 870
#4 (#1 OR #2 OR #3)
#5 rheumatoid next arthritis
#6 MeSH descriptor Arthritis, Rheumatoid explode all trees
#7 (#5 OR #6)
#8 (#4 AND #7)
Search date: 2009-February 12, 2013

Appendix 5. SCOPUS search strategy

Search strategy for benefits:
SCOPUS will be searched up to August of 2007, without limits of years:
KEY((certolizumab OR cimzia OR CDP-870 OR CDP870 OR "CDP 870") AND ("rheumatoid arthritis"))
Web of Knowledge (WOK), was searched up to August of 2007, without limits of years. The search strategy is as follows:
topic=((certolizumab OR cimzia OR CDP-870 OR CDP870 OR "CDP 870") AND ("rheumatoid arthritis")
Databases=MEDLINE, Current Contents Connect, Web of Science, Derwent Innovations Index, ISI Proceedings; Timespan=All Years
Search date: 2009-February 12, 2013

Appendix 6. TOXLINE (TOXNET) search strategy

Search strategy for safety:
TOXLINE (TOXNET) will be searched up to October 2007. The search strategy will combine index and text terms for CDP870:
#1. certolizumab OR "certolizumab pegol" OR CDP870 OR CDP-870 OR "CDP 870" OR cimzia
Search date: 2009-February 12, 2013

Appendix 7. Web of Knowledge

Web of Knowledge (Science Citation Index and Social Science Citation Index) 1900 - February 2013

Search terms: TS= (certolizumab OR cimzia OR or CDP870 OR cdp 870) and ("rheumatoid arthritis")
Search date: 2009-February 12, 2013

Appendix 8. Results of searches

Database name and coverage	Search date	Total Retrieved
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present	2009-February 12, 2013	315
Ovid Embase Classic+Embase 1947 to 2013 January 16	2009- February 12, 2013	1365

(*Continued*)

Wiley Cochrane Library - CENTRAL Issue 1 of 12- Jan. 2013	2009- February 12, 2013	11
EbscoHost CINAHL 1982-January 2013	2009- February 12, 2013	32
Toxline (TOXNET)	2007- February 12, 2013	34
Web of Knowledge	2009- February 12, 2013	189
SCOPUS 1966 to 2013 January	2009- February 12, 2013	814
	Total	2760
	Total without Duplicates	1300

Appendix 9. Searches updated to June 2014

Database name and coverage	Search date	Total Retrieved	Total without Duplicates
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE (R) 2013-2014	June 5, 2014	29	28
Ovid Embase Classic+Embase 2013-2014	June 5, 2014	208	192
EbscoHost CINAHL 2013-2014	June 5, 2014	1	1
Wiley Cochrane Library - CENTRAL 2013-2014	June 6, 2014	4	4
SCOPUS 2013-2014	June 10, 2014	233	124
Web of Knowledge 2013-2014	June 10, 2014	94	54

(*Continued*)

	Total	569	403

WHAT'S NEW

Last assessed as up-to-date: 5 June 2014.

Date	Event	Description
5 June 2014	New citation required but conclusions have not changed	In the current update, we changed some authors in the team: Sylvia Bort, Paloma Vela and Francis Kynaston are new
5 June 2014	New search has been performed	• Eleven trials were included (10 trials for benefits, 5 more than previously, and 10 for harms, 4 more than previously). We have more information regarding the quality of trials because UCB gave us data about this. This information has been used to update the assessment of the quality of trials. • New data from clinical trial 014, as Disease Activity Score (DAS) remission and SF-36 physical and mental domains or pain assessment, were added. We also added more data on the quality of the two phase II (004 and Choy) trials. • We got unpublished information on new trials for quality and results including withdrawals and serious adverse events from http://clinicaltrials.gov. We checked this information with UCB.

HISTORY

Protocol first published: Issue 1, 2009

Review first published: Issue 2, 2011

Date	Event	Description
3 April 2008	New search has been performed	CMSG ID: C001-R

CONTRIBUTIONS OF AUTHORS

Design the protocol: Juan Cabello; Vicente Ruiz; Amanda Burls

Write up the background: Paloma Vela

Develop the search strategy: Tamara Rader

Trial search (2 people): Vicente Ruiz; Sylvia Bort

Obtain copies of the trials: Sylvia Bort

Selection of trials for inclusion (2 + 1): Vicente Ruiz; P Jobanputra. If data discrepancies were to be resolved by involvement of a third person: FJB Kynaston-Pearson

Retrieval of trial data on benefits (two people): Vicente Ruiz; P Jobanputra. If data discrepancies were to be resolved by involvement of a third person: Francis JB Kynaston-Pearson

Data input in Revman: Sylvia Bort

Carry out analyses: Vicente Ruiz;

Interpret analyses: P Jobanputra

Write up results: Vicente Ruiz; P Jobanputra; P Vela; Amanda Burls; Juan Cabello; Sylvia Bort; FJB Kynaston-Pearson

Update review: Vicente Ruiz; P Jobanputra; P Vela

DECLARATIONS OF INTEREST

UCB paid Dr Vicente Ruiz's registration for the Cochrane meeting in Madrid 2011 to. In 2011 and 2012 he attended the UCB Advisory Board meetings in Madrid when the sponsor explained details and preliminary results for the new trials of certolizumab pegol. He did not receive any economic or other kind of compensation for these meetings.

Paresh Jo: UCB arranged and paid for travel and accommodation for the American College for Rheumatology meeting in Philadelphia in 2009.

Burls A: none known.

Cabello JB: none known.

Vela Casasempere P: I have participated as a member of advisory boards for Roche and Pfizer. I have also received fees for development of educational presentations for Roche, Abbvie, UCB, BMS and MSD, and travel and accommodations expenses to attend scientific meetings from Pfizer, Abbvie and Roche.

Bort-Marti S: none known.

Kynaston-Pearson FJB: none known.

SOURCES OF SUPPORT

Internal sources

- Grant from, Spain.

Instituto de Salud Carlos III. Ministerio de Sanidad. FIS number PI08˙90617 in the first previous systematic review.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Data synthesis

We decided to perform a random-effects model analysis despite low values of the I^2 statistic. Although it was the same drug, there is clear clinical heterogeneity (different doses, allowing MTX or not, different follow-up, different duration of RA, etc.).

Subgroup analysis

Subgroup analyses were planned for the duration of the illness (approximately three years evolution), patients' sex, drug dose and administration, and methodological quality; but only subgroup analysis regarding the dose of certolizumab pegol was performed. All phase III trials were performed in patients with a long mean duration of RA (from 6.1 to 9.5 years) and we could not obtain any data categorized by sex. All phase III trials allowed previous DMARD treatment (mean 1.2 to 2 years). All the phase III trials included in the meta-analysis were rated as high quality and so we did not perform subgroup analysis based on methodological quality.

INDEX TERMS

Medical Subject Headings (MeSH)

Antibodies, Monoclonal, Humanized; Antirheumatic Agents [*therapeutic use]; Arthritis, Rheumatoid [*drug therapy]; Immunoglobulin Fab Fragments [*therapeutic use]; Methotrexate [therapeutic use]; Polyethylene Glycols [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans